VOLUME 16 | NUMBER 11 | NOVEMBER 2022 | WWW.THE-RHEUMATOLOGIST.ORG

THE Rheumatologist®

An official publication of the ACR and the ARP serving rheumatologists and rheumatology professionals

RHEUMINATIONS™

Diagnosis by AI

Exploring the role of artificial intelligence in rheumatology

■ BY BHARAT KUMAR, MD, MME, FACP, FAAAAI, RHMSUS

I looked at the joints. They spoke back to me—"I need more humanism," they whispered.

To longtime readers, those two sentences may sound both familiar and alien, perhaps even a little humorous. That's because those sentences were generated entirely by a computer using artificial intelligence (AI). It was simple, too: I just copied the text of 120 previous Rheuminations columns and entered them into a freely accessible, online AI software program (GPT-3).[1] Nine lines of code and two clicks later, the computer "wrote" an entirely new, fantastical 1,067-word article.

Rheuminations columns are only the beginning of the AI revolution. Artificial intelligence, to those who may be unaware, is "the capacity of a computer to perform operations and tasks analogous to learning and decision making in humans."[2] AI is doing things, such as reading X-rays and diagnosing skin cancers, that we thought previously impossible for unsupervised machines to do.[3,4]

As AI becomes more precise and reliable, there is no question that AI will have profound effects on the field of rheumatology, from direct clinical service to education, research and beyond. Should we be excited—or worried? Let's rheuminate.

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SPEAK OUT RHEUM: *Guest Columnist*

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HOW DID WE GO SO WRONG WITH OPIOID PRESCRIBING?

■ BY RICHARD BRASINGTON JR., MD, FACP, MACR

I have been listening to *The Fighter Pilot Podcast* because my fantasy career would have been to fly a jet fighter plane (not even remotely possible, given my constitution). I learned that when an aircraft accident occurs, a *mishap board* is convened, not to assign blame but to try to learn what went wrong and avoid another mishap.

We should apply the same process to medical practices that were once considered good medical practice, but later were deemed undesirable. The liberal prescribing of high-dose chronic opioids is a good example.

When I began medical school in 1976, many things we now take for granted did not yet exist: computerized tomography and magnetic resonance imaging scans, effective medications for peptic ulcer disease and viral hepatitis, laparoscopic surgery, monoclonal antibody therapies, third-generation cephalosporins, the diagnosis of human immunodeficiency virus and its therapies, and on and on.

The chronic administration of opioid pain relievers would also be on that list. In the fullness of time, we have all realized that prescribing opioids over the long term in high doses for chronic pain was a bad idea. I have given a lot of thought to the question of how *We*—the medical profession and society in general—could have gotten this so wrong.

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AWARDS

The 2022 ARP President's & Merit Awards; Plus the ACR Recognizes Distinguished Fellows

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GLOBAL MEDICINE

Medical Mission to Ukraine

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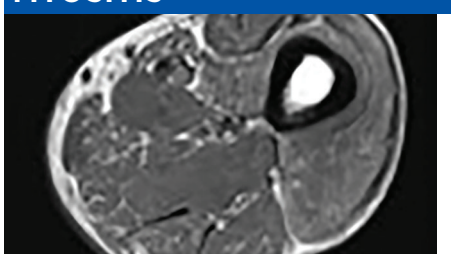
MYOSITIS



Thousand-Word Pictures

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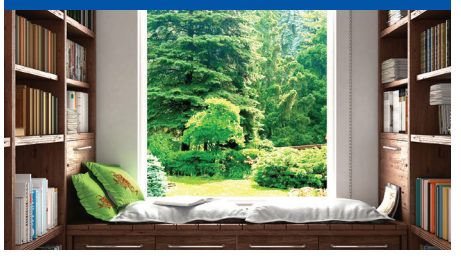
READING RHEUM



MoCA as a Screening Test in SLE & More

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SPEAK OUT RHEUM

To Prescribe Is Humane

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NOW APPROVED **FOR ACTIVE ANKYLOSING SPONDYLITIS (AS) IN ADULT TNFi-IR PATIENTS[1]**

POWERFUL DISEASE

INDICATION[1]

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

SAFETY CONSIDERATIONS[1]

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

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

ASAS=Assessment of SpondyloArthritis international Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; bDMARD=biologic disease-modifying antirheumatic drug; IR=intolerance or inadequate response; NSAID=nonsteroidal anti-inflammatory drug; TNFi=tumor necrosis factor inhibitor.

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RINVOQ®
upadacitinib

A once-daily oral therapy[1]

CONTROL IN AS

Nearly Half (44.5%) of AS bDMARD-IR Patients Achieved ASAS40 Primary Endpoint at Week 14 (vs placebo 18.2%, *P*<0.0001)[1,2,a]

DEFY EXPECTATIONS

Challenge treatment goals in AS

RinvoqHCP.com/AS

[a]SELECT-AXIS 2 study 1 was a 14-week, double-blind, parallel-group, placebo-controlled phase 3 study of 420 patients with active AS who had an intolerance or inadequate response to at least 2 NSAIDs and 1 or 2 bDMARDs. Patients could continue background NSAIDs. Patients were randomized to receive RINVOQ 15 mg once daily or placebo. Primary endpoint at Week 14: ASAS40 response vs placebo. [RINVOQ, n=211; placebo, n=209]

ASAS40 = ≥40% improvement and an absolute improvement from baseline of ≥2 units on a scale of 0 to 10 in at least 3 of the 4 domains, with no worsening in the fourth domain: total back pain, inflammation (mean score of BASDAI questions 5 and 6 on severity and duration of morning stiffness), physical function (BASFI), and Patient Global Assessment of disease activity.

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

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

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

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

Other Serious Adverse Reactions: Hypersensitivity Reactions (anaphylaxis and angioedema), Gastrointestinal Perforations, Laboratory Abnormalities (neutropenia, lymphopenia, anemia, lipid elevations, liver enzyme elevations), and Embryo-Fetal Toxicity.

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

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

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with RINVOQ® (upadacitinib) 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.

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.

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.

References: 1. RINVOQ [package insert]. North Chicago, IL: AbbVie Inc; 2022.
2. Data on file, AbbVie Inc. ABVRRTI73541.

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

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

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

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

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 228 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.

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 $AUC_{0\text{-}t}$ 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, and Ankylosing Spondylitis

The safety and effectiveness of RINVOQ in pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis 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.

Renal Impairment

For patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, 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, or ankylosing spondylitis.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, and ankylosing spondylitis, 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.

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Ref: 20071734 Revised: April 2022

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THE Rheumatologist®

VOLUME 16 | NUMBER 11 | NOVEMBER 2022

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The Rheumatologist (ISSN: 1931-3268, print; 1931-3209, online) is published monthly on behalf of the American College of Rheumatology by Wiley Periodicals LLC, 111 River Street, Hoboken, NJ 07030-5774. Postmaster, send address changes to Circulation Manager, *The Rheumatologist*, Wiley Periodicals LLC, c/o The Sheridan Press, P.O. Box 465, Hanover, PA 17331. Printed in the United States by Sheridan of Ohio (SOH), Brimfield, OH.

DR. BHARAT KUMAR

Rheumatologists, along with other clinicians and patients, need to engage with computer scientists to ensure that AI software not only mimics our collective thought patterns, but also upholds our collective values, such as diversity, equity & inclusion.

Reality Check

It's not just the intelligence that is artificial.

Before we explore how rheumatology professionals see AI, it may be worthwhile to investigate how AI views rheumatology professionals. To do so, let's visit an AI engine called DALL-E mini.[5]

DALL-E mini is AI software that creates totally new pictures based on what it has learned from a gigantic database of images. When I typed in "rheumatologist," I was excited to see that DALL-E mini had generated nine pictures of white-coat-clad rheumatologists palpating various joints. But this excitement turned to worry as I realized that each blurry-faced virtual rheumatologist was, as far as I could tell, white and male. Even after resubmitting five times, not a single non-white or non-male rheumatologist showed up in the 45 images.

It's a great example of how AI can mimic not only our intelligence but the foolishness of our societal biases.[6] Indeed, without strict scrutiny, implementation of AI can entrench societal divides and injustices. Rheumatologists, along with other clinicians and patients, need to engage with computer scientists to ensure that AI software not only mimics our collective thought patterns, but also upholds our collective values, such as diversity, equity and inclusion.

Error 404

Patient not found

This quick example with DALL-E demonstrates that AI may amplify known, existing biases. Yet AI can also generate new biases that we could not have even imagined before. Rheumatology is a field whose practice demands a sense of humility and creativity, something that cannot, at this time, be easily coded into machines. Our classification criteria are not meant to be unfailing algorithms for machines to faithfully implement; as such, a degree of misclassification is inevitable.[7] Moreover, we still don't quite understand the immunopathogenesis of many diseases and make several assumptions to fill in those gaps. Therefore, asking AI to engage in diagnostic decision making based on these assumptions without stringent external validation may lead to unforeseen harms.[8]

Some intrepid researchers are starting to engage in this painstaking validation process. For certain purposes, such as predicting response to methotrexate in rheumatoid arthritis patients, AI has shown great promise.[9] But when tasked with other high-stakes clinical decisions, such as predicting the diagnosis of ankylosing spondylitis, the results show a need for more refinement and validation.[10]

The precision of such technology will continue to advance, but what degree of imprecision will we be able to tolerate? After all, these are patients whose lives we are placing into the responsibility of computers with algorithms so convoluted their own programmers don't know how they work.[11] When a patient doesn't quite fit into an algorithm, how will AI cope? And what are the legal and ethical ramifications of outsourcing our clinical decision making to a computer?[12]

These questions will need to be explored further as AI encroaches more and more upon the duties and tasks originally intended purely for humans.

The Robot Will See You Now

Even then, even if we reach the point that AI can reliably make clinical decisions, we will need to ponder the ramifications on our healthcare workforce. Per the ACR's 2015 workforce assessment, there will be a deficit of more than 4,800 rheumatology providers by 2030.[13] It is very well possible that sophisticated AI-based algorithms can help address this crisis.

Existing rheumatology clinicians may be better able to use AI to automate burdensome and tedious tasks so direct patient care can be prioritized. Similarly, AI can help to support diagnostic decision making to facilitate care so that greater numbers of patients can be seen promptly. At its most ambitious, AI may support primary care providers in identifying those at risk for diagnostic delays or undertreatment, obviating even the need for a rheumatologist.[14]

But we've heard these sorts of promises before, with electronic health records (EHRs). And although EHRs have been quite helpful, the burden of documentation and administrative work has been a major driver of burnout, a contributor in and of itself to the workforce crisis.[15] If clinicians and patients are not in the driver's seat in programming and implementing AI for real-world clinical settings, I anticipate more administrative tasks, clicks and overall waste, furthering our burnout. And this doesn't even get into the very real potential of clinicians having to complete prior authorizations and peer-to-peer requests through an AI-powered insurance robot.[16]

The Joints Were Right

We need more humanism

I confess: When I initially read how the joints whispered to the clinician that they needed more humanism, I thought "What clichéd nonsense is this?" But the more I thought about it, the more I realized that the machine actually proposed the only path for rheumatology professionals to balance the risks and benefits of AI: We have to wholeheartedly embrace our own humanism. At this point in time, we need to ensure the greater efficiency provided by AI will afford us more agency to be humanistic to those whispering joints—and the humans that use them.

Altogether, this means we must prioritize our engagement with AI. Important first steps include increasing funding for research on informatics, artificial intelligence and machine learning, bolstering information technology support for clinical divisions, training fellows to familiarize themselves with AI and scrutinizing quality improvement work to ensure it embraces the principles of human-centered design. Moreover, we have to do this promptly, or events may swiftly overtake us. This is exemplified by the last, seemingly ominous, words of that AI-generated Rheuminations column: *The joints were happy and satisfied. Humanism prevailed, at least for the day.* **R**

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Truth-Telling

A testimony of racism's impact on patient-provider relationships

■ **BY MIA TAYLOR CHANDLER, MD, MPH**

"I tell everyone who comes into her room now, 'You will not disrespect my daughter again. No one will,'" recounts Sarah's mother. "Every time a [provider] acts rude to her, Sarah tells me, 'Ma, I'm used to it now,' and I have to insist 'No! Baby, you should never get used to that.' … Dr. Chandler, we went to the hospital over and over again, and we never got the right help until she was almost dying. We went there, and she was not treated either time. No blood was taken, and there was no pain medication given. They said, 'Follow up with dermatology for eczema.' She had ulcerations down to the bone and was in a lot of pain. We sat up in that emergency department and begged to be admitted. They did nothing to address her pain. Nothing."

After nine months of symptoms, which included a 15 kg weight loss, progressive muscle weakness, arthralgias and skin lesions, 13-year-old Sarah presented to the outpatient rheumatology clinic unable to hold her neck up or stand. She had dysphasia with excessive pooling of saliva; a hoarse, barely audible voice; deep skin ulcerations; severe oral thrush; intestinal bleeding; and periorbital swelling.

Sarah was eventually diagnosed with anti-melanoma differentiation-associated gene 5 (MDA5) positive juvenile dermatomyositis (JDM), an inflammatory myopathy manifested by muscle inflammation, weakness, skin rashes and rapidly progressive, and often fatal, interstitial lung disease.[1]

Just six months earlier, Sarah was moving about in the fullness of her life, playing with fashion dolls and plotting mischievously with her twin brother. She and her twin are the youngest of seven children. Sarah's mother hails from a line of clergy. Her maternal grandfather, with whom they share their dwelling space, is a pastor, as are several maternal aunts and uncles. Her paternal grandmother was a social worker and community activist in one of the city's historically redlined neighborhoods (i.e., a discriminatory practice in which services—financial and otherwise—are withheld from potential customers who reside in neighborhoods classified as *hazardous* to investment).[2-4] Her father has continued this legacy of service with a multi-decade-long career as an athletic director at a community center. Sarah's parents were among the early cohorts of children in the 1970s to take part in public school busing programs.[5]

This family knows racism and can readily see it in both its blatant and subtle forms. It is felt in some way every day. *Racism*, we know, is sometimes unconscious. It is "a belief in the inferiority of a person caused by prejudice against their ethnicity or phenotypic characteristics."[6] *Racial discrimination* is the "behavioral component of racism that manifests as differential treatment across various contexts such as interpersonal situations, systems and structures, and institutions."[6]

Brooke A. Cunningham, MD, PhD, a general internist, sociologist and assistant professor in the Department of Family Medicine and Community Health, University of Minnesota, Minneapolis, writes, "Black and Brown mothers have concerns that white mothers do not. We stand watch over our children as this world tries to deny their beauty, thwart their genius, dim their light and too quickly take their innocence. We know the day will soon come when we will have to dry their tears and remind them that they are everything. We hold them tight, because we know there will be other days when we will not be there to comfort them."[7]

Sarah's mother continues, "We were just having this conversation a few months before all of this happened with Sarah. Saying to each other, you wouldn't believe how many Black people are not taken seriously while at the [doctors' office]. Another daughter was just about to have a baby and, knowing they don't take Black women seriously, she had fears about her risk of dying in childbirth. This is truth-telling."[8]

Repetitive experiences of perceived or blatant discrimination in daily life—and especially during healthcare encounters—can condition one to distrust the healthcare system and the people within it. Presenting for care can, paradoxically, pose a threat to life and dignity. The healthcare setting is, thus, inherently provocative for Sarah's family and others who are keenly aware of racism and racial health disparities in the U.S.

Disparities

Disparity is a term used to address *avoidable* differences.[9] Unequal health outcomes are not inherently unjust because they can arise from biology or chance.[10] Disparities are "linked to social, economic, or environmental disadvantages and are fueled by bias or discrimination at the individual, institutional, and health care system levels."[11] They are "differences between groups who have systematically experienced greater obstacles to health based upon gender, age, race, ethnicity, religion, mental or physical ability, and geographic location compared to the majority population."[11]

Notable racial, ethnic, socioeconomic and geographic disparities exist in care delivery, comorbidities and adverse outcomes among individuals with rheumatic diseases.[12-14]

"I used to love the medical field," Sarah's mother continues. "I've been working in it since I was 16, but I don't trust them even for myself. After what I saw and experienced for months with Sarah, I don't know if I can get [that trust] back. Every time I walk through those doors now, sadness, anger and fear come down like a flood all over me. If I could go somewhere else, I would go."

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DR. CHANDLER

Deterrents to Seeking Healthcare

Experiences of racism and poor communication are deterrents to seeking healthcare, even when available.[15,16] What Sarah's mother displays is the stress response from racialized trauma incurred at the individual and structural levels.[17,18] Racial trauma refers to "stress responses and reactions to racialized incidents including the perceived or real threat of harm and injury, humiliating and shaming events, and witnessing racial discrimination towards oneself or other minoritized people."[19]

Sarah's mother has identified those of us she can trust. We are those from whom she feels the verbal and non-verbal communications authentically convey honor, respect and validation of her lived experience and shared humanity. We are those from whom she does not perceive the imminent threat of humiliation, shame or discrimination.

Despite the emotional trauma incurred and her misgivings about the healthcare institution, Sarah's mother brings her daughter back biweekly for care, and Sarah's condition has dramatically improved. She is walking without assistance and attending to most of her activities of daily living.

After an induction course of intravenous cyclophosphamide (*Note*: mycophenolate mofetil could not be readily absorbed), Sarah is on a complex, but effective, maintenance regimen of multiple immunomodulating medications that include intravenous immunoglobulin infusions, hydroxychloroquine and tofacitinib.

"What stands between a disrespected African American and the source of

continued on page 10

> Racial concordance is a proxy for the degree to which patients & their unique circumstances are seen, heard & respected as fundamentally human.

 continued from page 9

Repetitive experiences of perceived or blatant discrimination in daily life—& especially during healthcare encounters—can condition one to distrust the healthcare system & the people within it.

disrespect is almost 400 years of history, four centuries of being the target of humiliation and abuse," writes Joy DeGruy, a sociologist and author of the book *Post Traumatic Slave Syndrome: America's Legacy of Enduring Injury and Healing*. "A history of racial conflict, inequality and contempt culminates in a moment that few people not of this culture could comprehend, let alone predict. Yet every [Black American with multigenerational roots in this country] who has witnessed or heard of incidents like this understands the unspoken and ubiquitous cultural law that was operating."[20]

Relationship Dynamics

I am Sarah's primary rheumatology provider, and I share racial and cultural concordance with her family. However, not all providers on the "trusted" list do. One need not be Black to know the *ubiquitous cultural law* mentioned above. Greater emphasis on the quality of patient-provider communication and relationships may be an effective way to remove barriers to healthcare access.

Providers can consciously behave in ways that improve relationship dynamics when faced with justified apprehension, by using the knowledge that honor, respect and authenticity are paramount. It is also important to be mindful of the verbal and non-verbal language cues that convey when one isn't regarded as inherently equal in human value to all others.

Paradigm Shift

We in America have been summoned to account for centuries of relational harm to minoritized peoples. Members of the rheumatology professional community are not excused from this national reckoning and must actively participate.[21] We can no longer ignore or give passive attention to the striking lack of diversity in the rheumatology workforce or the underrepresentation of racial and ethnic minorities in clinical trials and disease registries, despite the increased prevalence of diseases like lupus in this population.[22]

Black physicians comprise approximately 4% of the total physician workforce, 1.3% of pediatric rheumatology providers and 0.8% of adult providers.[23,24] These numbers provide indisputable evidence that the field of rheumatology's relationship with minoritized peoples is severely flawed.

Although provider-patient concordance has been shown to improve patient satisfaction and quality of care, I believe that racial concordance is a proxy for the degree to which patients and their unique circumstances are seen, heard and respected as fundamentally human.[25] We all are human; therefore, each person of sound mind has the capacity to empathize, to evaluate prejudiced thought patterns and then act with empathy to remove the barriers of racism for the sake of delivering more excellent care.

Advocates focus intensively on sweeping policy change at organizational and government levels to address inequities in the healthcare system. Policy reform is an essential component for promoting health equity; however, since the inception of the American democracy, grand policy changes have not addressed the root cause of weak relationships between racially or ethnically discordant parties.

The solution for eradicating racism—and other *-isms* that drive many systemic inequities—are not fixed by policy changes. The resolution of America's most challenging issue demands a paradigm shift that requires everyone to advance in inner work.

Racism is an issue of morality. If we strive to believe in the inherent nobility and the equal human value of all persons, regardless of race, gender, class, economic, educational, intellectual or ability status, then our inner thoughts will transform our outer behavior—priorities, professional processes and policies—collectively into what will be reflective of the ideals of equity and justice in all facets of rheumatology. **R**

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Acknowledgments: Thanks to Candace Feldman, MD, ScD (Brigham and Women's Hospital, Boston), and Mary Beth Son, MD, MSc (Boston Children's Hospital), for their reviews and suggested edits.

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Clinical Academic Rheumatology Generates Profits for Health Systems

■ **BY LARA C. PULLEN, PHD**

A retrospective study of five practicing academic rheumatologists at the Loma Linda University School of Medicine, California, revealed that for every dollar billed in an office visit, $12.14 was generated in downstream revenue to the health system.[1]

Kathleena M. D'Anna, DO, a fellow in the Division of Rheumatology at Loma Linda, and colleagues adjusted the documented downstream revenue for inflation and found it was comparable to that calculated in 2005 by Wickersham et al. (i.e., $10.02 for every $1.00 billed).[2] However, the authors write that the study by Wickersham et al. was performed in Colorado, where reimbursement rates based on Medicare data are lower than in Southern California.

Infusion of Biologics Drives Profits

In the 15 years since the Wickersham study, the field of rheumatology has experienced an increase in the number of biologic agents available to treat patients, as well as an increase in the incorporation of diagnostic tools, such as ultrasound and targeted blood markers.[3]

The investigators designed the study to determine if the relationship between direct clinical services rendered by a rheumatologist through patient care and the downstream revenue earned by a hospital system from these encounters had changed from 2005 to 2020. Their study included only revenue generated by available Medicare allowable charges. The authors note that although Loma Linda University Hospital participates in the 340b pricing program that helps make healthcare and prescription drugs more affordable, discounted prices were proprietary and inaccessible to the researchers. Thus, the team estimated 340b cost to be 60% of published wholesale acquisition prices.

Although the investigators found the downstream revenue remained stable from 2005 to 2020, they documented an overall increase in the dollar amount generated from laboratory studies, radiology and consults with other specialists when compared with the 2005 Wickersham study. The main driver of the downstream revenue in the current study, as well as the Wickersham study, was infused medications. However, the authors note their study likely underestimates infusion revenue because their hospital—like most hospitals—lacks transparency on billing processes for such procedures.

Cognitive Specialists Undervalued

The investigators found academic rheumatologists averaged an annual production of 4,755 work relative value units (wRVUs), which is similar to that averaged by private practice rheumatologists (4,821 wRVUs).[4] This finding means that although academic researchers have academic obligations outside medical care, they appear to have very little time set aside for such activities. The researchers explain in their discussion that academic rheumatologists may find it difficult to balance their demanding outpatient clinical practice treating chronic and com-

continued on page 35

Updates from the ACR Insurance Subcommittee

■ **REBECCA SHEPHERD, MD, MBA, FACR, FACP**

As rheumatologists, we often experience trials and tribulations set forth by insurance payers. I know these challenges all too well from my own practice.

Rheumatologists are critical to the well-being of so many patients who struggle day in and day out with autoimmune diseases and other joint complaints. We have new medications and interventions that allow us to help our patients, but all too often we spend our limited time justifying our decisions—essentially because of payers' desires to limit the cost of care. Just last week, I spent time explaining to a payer that apremilast is not a biologic and can be used safely with tumor necrosis factor inhibitors. As chair of the Insurance Subcommittee (ISC) of the ACR's Committee on Rheumatologic Care, I have the honor of working alongside our knowledgeable and hard-working ACR staff as they advocate for our membership and educate payers on clinical matters.

The ISC serves as a critical force to educate payers as we advocate for policies that prioritize fair and appropriate access to rheumatology care and treatment. I wanted to share the following updates on some of our recent efforts.

Medicare Reimbursement for Administration of Biologics

- As of July 2022, all Medicare Administrative Contractors (MACs) have enacted Local Coverage Articles (LCAs) prohibiting the use of complex chemotherapy administration codes with Cimzia, Orencia, Simponi Aria, Stelara and Prolia. The ACR has spoken with each of the MACs; however, they are unwilling to revise their policies.
- The ACR strongly opposes the downcoding of these drugs. We have also argued that the use of LCAs—as opposed to local coverage determinations (LCDs)—to enact these changes undermines transparency and stakeholder engagement.
- The ACR recently spearheaded a coalition effort to address the flawed policymaking process used to implement these changes. In June, the ACR led a multispecialty sign-on letter to the Centers for Medicare & Medicaid Services (CMS) asking them to compel the MACs to discontinue the inappropriate use of LCAs and invalidate all current LCAs that restrict coverage or patient access.
- The CMS acknowledged the concerns raised and suggested this specific issue may fall under the purview of its Center for Program Integrity (CPI). The ACR has subsequently reached out to the CPI and will pursue additional opportunities for dialogue.

Cigna Modifier 25

This modifier is defined as a significant, separately identifiable evaluation and management (E/M) service by the same physician or other qualified healthcare professional on the same day of the procedure or other service.

- In the spring, Cigna announced that effective Aug. 13, claims billed with modifier 25 would be immediately declined unless accompanied by a full set of office notes. In doing so, Cigna would exacerbate the existing administrative burden on rheumatology practices.
- The ACR sent a letter to Cigna expressing concerns that the policy would result in inappropriate denials and/or delayed payments for legitimate services.
- Cigna subsequently delayed the policy indefinitely and we are continuing to monitor for further developments.

Prior Authorization

- We have heard from numerous members about challenges with increasingly burdensome prior authorization processes.
- CVS and Express Scripts were specifically noted for both the overall length of their forms and the irrelevance or redundancy of many questions.
- The ACR has engaged both CVS and Express Scripts in an ongoing dialogue aimed at streamlining prior authorization forms to reduce administrative burden and avoid potential delays in patient care.

The ISC is here to assist practices as they navigate challenging insurance issues. If you have concerns about a payer policy or would like help with an issue impacting your practice, complete the Health Plan Complaint Form or email **practice@rheumatology.org**.

Thank you for your investment in the greater community of our shared specialty. Together, we remain committed to delivering exceptional patient care. **R**

Rebecca Shepherd, MD, MBA, FACR, FACP, is the chair of the ACR Insurance Subcommittee of the Committee on Rheumatologic Care. She is chief of rheumatology and director of the osteoporosis service line at Lancaster General Health in Lancaster, Pa.

With Deepest Gratitude

The ACR appreciates your willing service

We acknowledge all ACR, ARP and Rheumatology Research Foundation volunteers whose committee terms are ending this month (https://tinyurl.com/2e4byepc). Thank you for your valuable time and efforts toward advancing rheumatology during a challenging time.

IN ADULTS WITH ACTIVE PSORIATIC ARTHRITIS (PsA)

When PsA leaves your patients with joints that **FEEL LOCKED IN STEEL**, help them...

EMERGE TREMFYANT®

Tremfya® (guselkumab)

In DISCOVER 2, ACR20 response at Week 24 (primary endpoint)

64% of patients receiving TREMFYA® q8w (159/248) achieved an ACR20 response vs 33% of patients receiving placebo (81/246) ($P<0.0001$)[1-3*†]

In DISCOVER 1, ACR20 response at Week 24 (primary endpoint)

52% of patients receiving TREMFYA® q8w (66/127) achieved an ACR20 response vs 22% of patients receiving placebo (28/126) ($P<0.0001$)[1,2,4*†]

*Through Week 24, patients were considered to be nonresponders after meeting treatment failure criteria: discontinued study agent for any reason, terminated study participation for any reason, initiated or increased the dose of disease-modifying antirheumatic drugs (DMARDs) or oral corticosteroids over baseline for PsA, or initiated protocol-prohibited medications/therapies for PsA. **After Week 24, treatment failure rules were not applied.**

†Patients with missing data were considered nonresponders.

Please see full study designs on the following page.

INDICATION

TREMFYA® (guselkumab) is indicated for the treatment of adults with active psoriatic arthritis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

TREMFYA® is contraindicated in patients with a history of serious hypersensitivity reaction to guselkumab or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with postmarket use of TREMFYA®. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, discontinue TREMFYA® and initiate appropriate therapy.

Infections

TREMFYA® may increase the risk of infection. Treatment with TREMFYA® should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated.

Consider the risks and benefits of treatment prior to prescribing TREMFYA® in patients with a chronic infection or a history of recurrent infection. Instruct patients receiving TREMFYA® to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection, or is not responding to standard therapy, closely monitor and discontinue TREMFYA® until the infection resolves.

janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Pre-Treatment Evaluation for Tuberculosis (TB)

Evaluate patients for TB infection prior to initiating treatment with TREMFYA®. Initiate treatment of latent TB prior to administering TREMFYA®. Monitor patients for signs and symptoms of active TB during and after TREMFYA® treatment. Do not administer TREMFYA® to patients with active TB infection.

Immunizations

Prior to initiating TREMFYA®, consider completion of all age-appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with TREMFYA®.

ADVERSE REACTIONS

Most common (≥1%) adverse reactions associated with TREMFYA® include upper respiratory infections, headache, injection site reactions, arthralgia, bronchitis, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections.

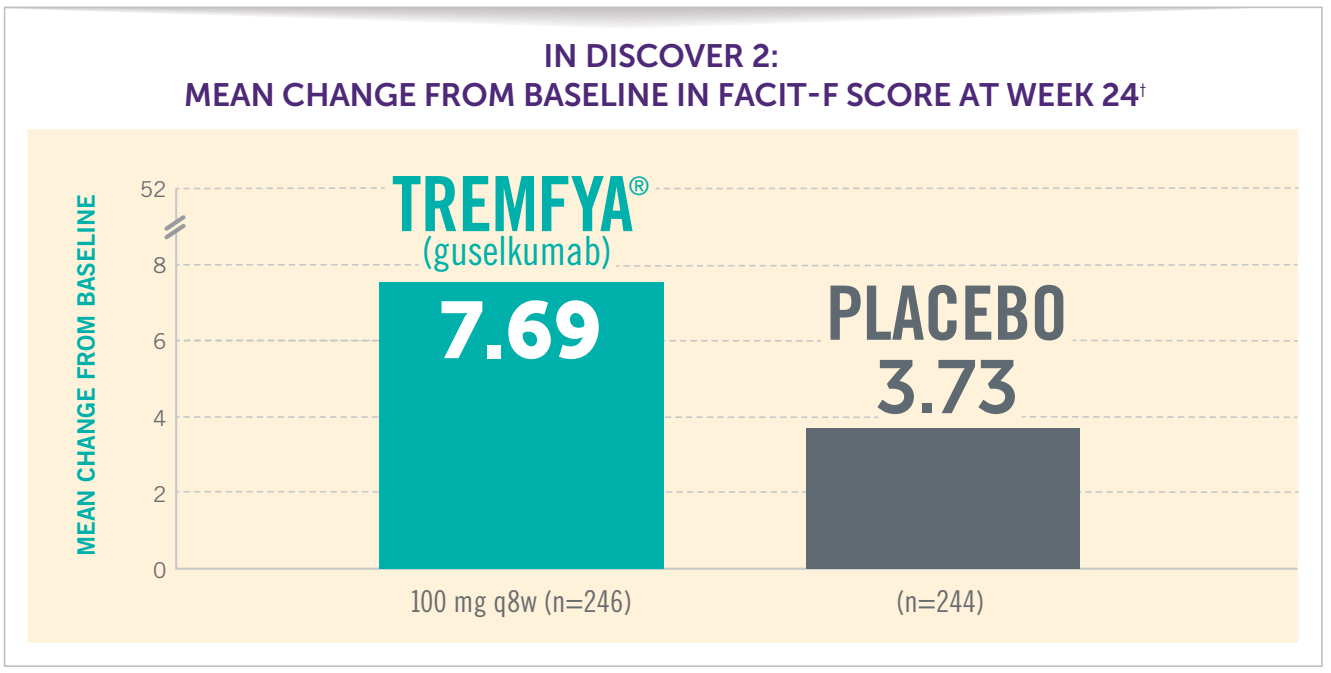
The overall safety profile observed in patients with psoriatic arthritis is generally consistent with the safety profile in patients with plaque psoriasis, with the addition of bronchitis and neutrophil count decreased.

Please see the Brief Summary of the full Prescribing Information within this ad.

cp-82625v3

TREMFYA® IS THE FIRST ALT-MOA* BIOLOGIC TO INCLUDE FACIT-F IN THE LABEL FOR ACTIVE PsA

TREATMENT WITH TREMFYA® RESULTED IN IMPROVEMENT IN FATIGUE AS MEASURED BY FACIT-F[1]



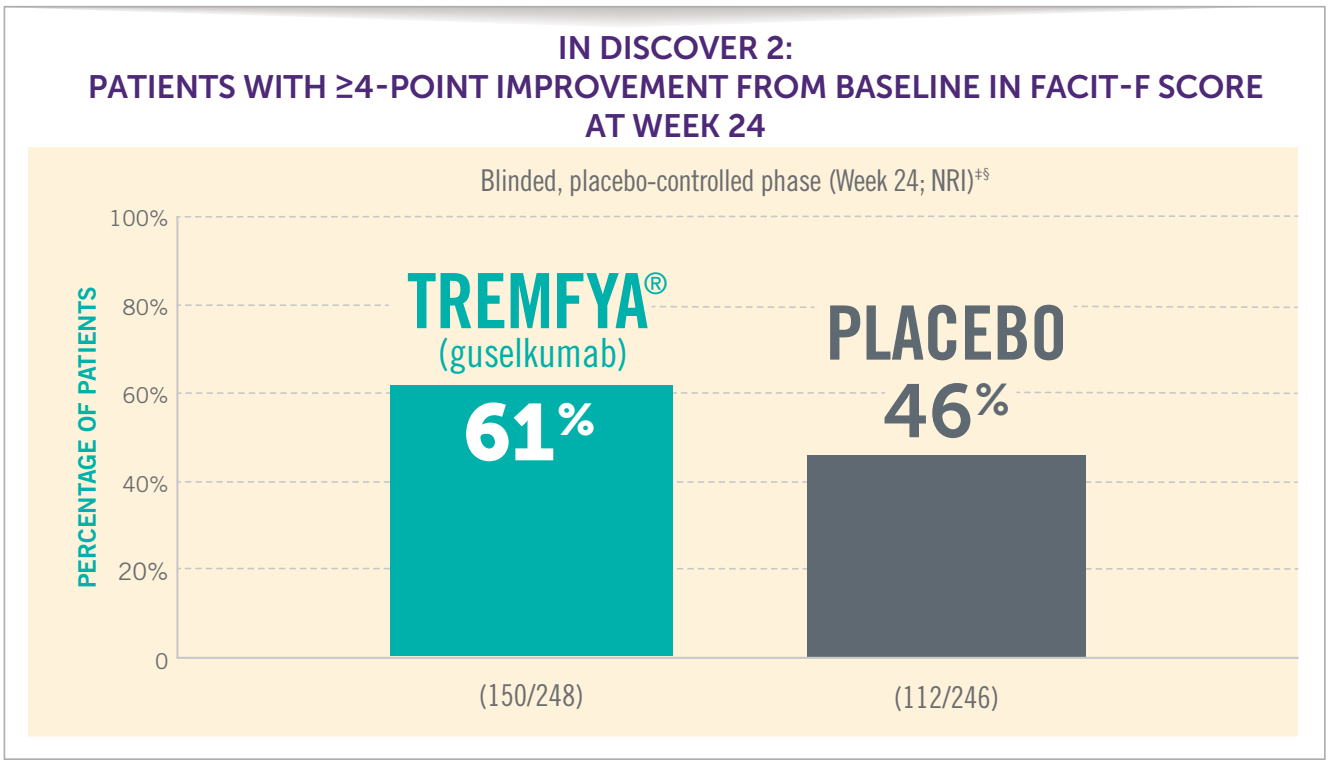
IN DISCOVER 1 AT WEEK 24

- The mean change from baseline in FACIT-F score was 5.76 for patients receiving TREMFYA® q8w (n=127) vs 2.15 for patients receiving placebo (n=126)[2†]

The FACIT-F endpoints in DISCOVER 1 and DISCOVER 2 were not adjusted for multiplicity. Therefore, statistical significance has not been established.

FACIT-F measures a patient's level of fatigue and tiredness over the last 7 days through a questionnaire consisting of 13 questions. Lower scores reflect more severe fatigue.[1,5]

≥4 POINT IMPROVEMENT FROM BASELINE IN FACIT-F SCORE



IN DISCOVER 1 AT WEEK 24

- The percentage of patients with ≥4-point improvement from baseline in FACIT-F score was 54% (68/127) for patients receiving TREMFYA® q8w vs 35% (44/126) for patients receiving placebo[1‡§]

The FACIT-F endpoints in DISCOVER 1 and DISCOVER 2 were not adjusted for multiplicity. Therefore, statistical significance has not been established.

The threshold for clinically meaningful improvement when assessing fatigue using FACIT-F in clinical trials was based on literature in PsA that supports a change of ≥4.[6]

FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue[5]; MOA=mechanism of action; NRI=nonresponder imputation.

*Alt-MOA is a biologic not classified as a tumor necrosis factor (TNF) blocker. TREMFYA® is an interleukin-23 (IL-23) blocker.[1]

†Through Week 24, patients were considered to have no improvement (change=0) after meeting treatment failure criteria: discontinued study agent for any reason, terminated study participation for any reason, initiated or increased the dose of DMARDs or oral corticosteroids over baseline for PsA, or initiated protocol-prohibited medications/therapies for PsA. **After Week 24, treatment failure rules were not applied.**

‡Patients who met any treatment failure criteria prior to the specific visit were considered as nonresponders at the said visit: discontinued study agent for any reason, terminated study participation for any reason, initiated or increased the dose of DMARDs or oral corticosteroids over baseline for PsA, or initiated protocol-prohibited medications/therapies for PsA. **After Week 24, treatment failure rules were not applied.**

§Patients with missing data were considered nonresponders.

DEMONSTRATED SAFETY PROFILE[2]

SAFETY PROFILE IN PsA ACROSS 2 CLINICAL TRIALS

TREATMENT-EMERGENT ADVERSE EVENTS REPORTED IN THE PLACEBO-CONTROLLED PHASE THROUGH WEEK 24: COMBINED ACROSS DISCOVER 1 AND DISCOVER 2

	Adverse Events	Serious Adverse Events	Infections	Serious Infections
TREMFYA® 100 mg q8w (n=375), n (%) [events per 100 patient-years of follow-up]	182 (48.5%) [257.30]	7 (1.9%) [4.04]	73 (19.5%) [58.27]	1 (0.3%) [0.58]
PLACEBO (n=372), n (%) [events per 100 patient-years of follow-up]	176 (47.3%) [220.01]	12 (3.2%) [9.26]	77 (20.7%) [58.48]	3 (0.8%) [4.05]

Initially evaluate for tuberculosis (TB) and monitor for signs and symptoms of TB infection during and after treatment. NO ROUTINE LAB MONITORING REQUIRED DURING TREATMENT.[1]

- The overall safety profile observed in patients with PsA treated with TREMFYA® is generally consistent with the profile in patients with plaque psoriasis, with the addition of bronchitis and neutrophil count decreased. In the 24-week, placebo-controlled period, combined across the 2 studies[1]:
  - Bronchitis occurred in 1.6% of patients in the TREMFYA® q8w group and 1.1% of patients in the placebo group
  - Neutrophil count decreased occurred in 0.3% of patients in the TREMFYA® q8w group compared with 0% of patients in the placebo group. The majority of events of neutrophil count decreased were mild, transient, not associated with infection and did not lead to discontinuation

TREMFYA® IS THE 1ST BIOLOGIC THAT SELECTIVELY INHIBITS IL-23 APPROVED FOR THE TREATMENT OF ADULTS WITH ACTIVE PsA

TREMFYA® is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. The clinical significance of these findings is unknown.[1]

VISIT **TREMFYAHCP.COM** TO LEARN MORE

Study Designs: DISCOVER 1 and **DISCOVER 2** were phase 3, multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of TREMFYA® administered q8w subcutaneously with starter doses at Week 0 and Week 4 (n=127 and n=248, respectively) or placebo (n=126 and n=246, respectively) with starter doses at Week 0, and then every 4 weeks in patients with active PsA (fulfilling CIASsification criteria for Psoriatic ARthritis [CASPAR] criteria) despite standard therapies (nonbiologic DMARDs), apremilast, and nonsteroidal anti-inflammatory drugs [NSAIDs]). A stable dose of 1 selected nonbiologic DMARD, corticosteroids, and NSAIDs was permitted but not required. In DISCOVER 1, eligible patients (≥18 years of age) had active PsA (swollen/tender joints ≥3, C-reactive protein [CRP] ≥0.3 mg/dL) for at least 6 months and included patients with a prior biologic experience of ≤2 anti-TNFα treatments. Patients with other inflammatory diseases and those who had previously received Janus kinase (JAK) inhibitors or biologics other than TNFα inhibitors were excluded. In DISCOVER 2, eligible patients (≥18 years of age) had active PsA (swollen/tender joints ≥5, CRP ≥0.6 mg/dL) for at least 6 months and no prior JAK inhibitor or biologic experience. At Week 16, patients in all treatment groups who had <5% improvement from baseline in both swollen and tender joint counts were considered as meeting early escape criteria and were allowed to initiate or increase the dose of one of the permitted concomitant medications up to the maximum dose allowed. In DISCOVER 1 and DISCOVER 2, 128 patients and 246 patients, respectively, were randomized to a q4w dosing regimen. TREMFYA® dosed every 4 weeks is not an approved dosing regimen. The primary endpoint in both DISCOVER 1 and DISCOVER 2 was ACR20 response at Week 24.[2-4]

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

References: 1. TREMFYA® (guselkumab) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc. **3.** Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naïve patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet.* 2020;395(10230):1126-1136. **4.** Deodhar A, Helliwell PS, Boehncke WH, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naïve or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet.* 2020;395(10230):1115-1125. **5.** Cella D, Yount S, Sorensen M, et al. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol.* 2005;32(5):811-819. **6.** Cella D, Wilson H, Shalhoub H, et al. Content validity and psychometric evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in patients with psoriatic arthritis. *Journal of Patient-Reported Outcomes.* 2019;3(30):1-12.

Tremfya® (guselkumab)

Brief Summary of Prescribing Information for TREMFYA® (guselkumab)
TREMFYA® (guselkumab) injection, for subcutaneous use
See package insert for full Prescribing Information.

INDICATIONS AND USAGE Plaque Psoriasis: TREMFYA® is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. **Psoriatic Arthritis:** TREMFYA is indicated for the treatment of adult patients with active psoriatic arthritis. **CONTRAINDICATIONS** TREMFYA is contraindicated in patients with a history of serious hypersensitivity reaction to guselkumab or to any of the excipients *[see Warnings and Precautions]*. **WARNINGS AND PRECAUTIONS Hypersensitivity Reactions:** Serious hypersensitivity reactions, including anaphylaxis, have been reported with postmarket use of TREMFYA. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, discontinue TREMFYA and initiate appropriate therapy. **Infections:** TREMFYA may increase the risk of infection. In clinical trials in subjects with plaque psoriasis, infections occurred in 23% of subjects in the TREMFYA group versus 21% of subjects in the placebo group through 16 weeks of treatment. Upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections occurred more frequently in the TREMFYA group than in the placebo group *[see Adverse Reactions]*. The rate of serious infections for the TREMFYA group and the placebo group was ≤ 0.2%. A similar risk of infection was seen in placebo-controlled trials in subjects with psoriatic arthritis. Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing TREMFYA. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and discontinue TREMFYA until the infection resolves. **Pre-treatment Evaluation for Tuberculosis:** Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TREMFYA. Initiate treatment of latent TB prior to administering TREMFYA. In clinical trials, 105 subjects with plaque psoriasis and 71 subjects with psoriatic arthritis with latent TB who were concurrently treated with TREMFYA and appropriate TB prophylaxis did not develop active TB. Monitor patients for signs and symptoms of active TB during and after TREMFYA treatment. Consider anti-TB therapy prior to initiating TREMFYA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Do not administer TREMFYA to patients with active TB infection. **Immunizations:** Prior to initiating therapy with TREMFYA, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with TREMFYA. No data are available on the response to live or inactive vaccines. **ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of labeling: • Infections *[see Warnings and Precautions]* • Hypersensitivity Reactions *[see Contraindications and 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. Plaque Psoriasis: In clinical trials, a total of 1823 subjects with moderate-to-severe plaque psoriasis received TREMFYA. Of these, 1393 subjects were exposed to TREMFYA for at least 6 months and 728 subjects were exposed for at least 1 year. Data from two placebo- and active-controlled trials (PsO1 and PsO2) in 1441 subjects (mean age 44 years; 70% males; 82% white) were pooled to evaluate the safety of TREMFYA (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 8 weeks). *Weeks 0 to 16:* In the 16-week placebo-controlled period of the pooled clinical trials (PsO1 and PsO2), adverse events occurred in 49% of subjects in the TREMFYA group compared to 47% of subjects in the placebo group and 49% of subjects in the U.S. licensed adalimumab group. Serious adverse events occurred in 1.9% of subjects in the TREMFYA group (6.3 events per 100 subject-years of follow-up) compared to 1.4% of subjects in the placebo group (4.7 events per 100 subject-years of follow-up), and in 2.6% of subjects in U.S. licensed adalimumab group (9.9 events per 100 subject-years of follow-up). Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TREMFYA group than in the placebo group during the 16-week placebo-controlled period.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects through Week 16 in PsO1 and PsO2

	TREMFYA[a] 100 mg N=823 n (%)	Adalimumab[b] N=196 n (%)	Placebo N=422 n (%)
Upper respiratory infections[c]	118 (14.3)	21 (10.7)	54 (12.8)
Headache[d]	38 (4.6)	2 (1.0)	14 (3.3)
Injection site reactions[e]	37 (4.5)	15 (7.7)	12 (2.8)
Arthralgia	22 (2.7)	4 (2.0)	9 (2.1)
Diarrhea	13 (1.6)	3 (1.5)	4 (0.9)
Gastroenteritis[f]	11 (1.3)	4 (2.0)	4 (0.9)
Tinea infections[g]	9 (1.1)	0	0
Herpes simplex infections[h]	9 (1.1)	0	2 (0.5)

[a] Subjects receiving 100 mg of TREMFYA at Week 0, Week 4, and every 8 weeks thereafter
[b] U.S. licensed adalimumab
[c] Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI.
[d] Headache includes headache and tension headache.
[e] Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, edema, pruritus, pain, discoloration, induration, inflammation, and urticaria.
[f] Gastroenteritis includes gastroenteritis and viral gastroenteritis.
[g] Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections.
[h] Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.

Adverse reactions that occurred in < 1% but > 0.1% of subjects in the TREMFYA group and at a higher rate than in the placebo group through Week 16 in PsO1 and PsO2 were migraine, candida infections, and urticaria. Specific Adverse Reactions: *Infections:* Infections occurred in 23% of subjects in the TREMFYA group compared to 21% of subjects in the placebo group. The most common (≥ 1%) infections were upper respiratory infections, gastroenteritis, tinea infections, and herpes simplex infections; all cases were mild to moderate in severity and did not lead to discontinuation of TREMFYA. *Elevated Liver Enzymes:* Elevated liver enzymes were reported more frequently in the TREMFYA group (2.6%) than in the placebo group (1.9%). Of the 21 subjects who were reported to have elevated liver enzymes in the TREMFYA group, all events except one were mild to moderate in severity and none of the events led to discontinuation of TREMFYA. *Safety through Week 48:* Through Week 48, no new adverse reactions were identified with TREMFYA use and the frequency of the adverse reactions was similar to the safety profile observed during the first 16 weeks of treatment. Psoriatic Arthritis: TREMFYA was studied in two placebo-controlled trials in subjects with psoriatic arthritis (748 subjects on TREMFYA and 372 subjects on placebo). Of the 748 subjects who received TREMFYA, 375 subjects received TREMFYA 100 mg at Week 0, Week 4, and every 8 weeks thereafter and 373 subjects received TREMFYA 100 mg every 4 weeks. The overall safety profile observed in subjects with psoriatic arthritis treated with TREMFYA is generally consistent with the safety profile in subjects with plaque psoriasis with the addition of

bronchitis and neutrophil count decreased. In the 24-week placebo-controlled period, combined across the two studies, bronchitis occurred in 1.6% of subjects in the TREMFYA q8w group and 2.9% of subjects in the TREMFYA q4w group compared to 1.1% of subjects in the placebo group. Neutrophil count decreased occurred in 0.3% of subjects in the TREMFYA q8w and 1.6% of subjects in the TREMFYA q4w group compared to 0% of subjects in the placebo group. The majority of events of neutrophil count decreased were mild, transient, not associated with infection and did not lead to discontinuation. **Immunogenicity:** As with all therapeutic proteins, there is the potential for immunogenicity with TREMFYA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to guselkumab across indications or with the incidences of antibodies to other products may be misleading. Plaque Psoriasis: Up to Week 52, approximately 6% of subjects treated with TREMFYA developed antidrug antibodies. Of the subjects who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing antibodies. Among the 46 subjects who developed antibodies to guselkumab and had evaluable data, 21 subjects exhibited lower trough levels of guselkumab, including one subject who experienced loss of efficacy after developing high antibody titers. Up to Week 156, approximately 9% of subjects treated with TREMFYA developed antidrug antibodies and of these subjects approximately 6% were classified as neutralizing antibodies. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions. Psoriatic Arthritis: Up to Week 24, 2% (n=15) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects, 1 had antibodies that were classified as neutralizing antibodies. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics, efficacy and safety of guselkumab. **Postmarketing Experience:** The following adverse reactions have been reported during post-approval of TREMFYA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to TREMFYA exposure. *Immune system disorders:* Hypersensitivity, including anaphylaxis *[see Warnings and Precautions] Skin and subcutaneous tissue disorders:* Rash *[see Warnings and Precautions]* **DRUG INTERACTIONS CYP450 Substrates:** The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, interferon) during chronic inflammation. Results from an exploratory drug-drug interaction study in subjects with moderate-to-severe plaque psoriasis suggested a low potential for clinically relevant drug interactions for drugs metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 but the interaction potential cannot be ruled out for drugs metabolized by CYP2D6. However, the results were highly variable because of the limited number of subjects in the study. Upon initiation of TREMFYA in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed *[see Clinical Pharmacology (12.3) in Full Prescribing Information].* **USE IN SPECIFIC POPULATIONS Pregnancy:** Pregnancy Exposure Registry: There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TREMFYA during pregnancy. Patients should be encouraged to enroll by calling 1-877-311-8972. Risk Summary: There are no available data on TREMFYA use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, TREMFYA may be transmitted from the mother to the developing fetus. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of guselkumab during organogenesis through parturition at doses up to 30 times the maximum recommended human dose (MRHD). Neonatal deaths were observed at 6- to 30-times the MRHD *(see Data)*. The clinical significance of these nonclinical findings is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated 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. Data: *Animal Data:* In a combined embryofetal development and pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of guselkumab up to 50 mg/kg (30 times the MRHD based on a mg/kg comparison) from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD based on a mg/kg comparison) and three monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD based on a mg/kg comparison). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age. **Lactation:** Risk Summary: There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREMFYA and any potential adverse effects on the breastfed infant from TREMFYA or from the underlying maternal condition. **Pediatric Use:** The safety and efficacy of TREMFYA in pediatric patients (less than 18 years of age) have not been established. **Geriatric Use:** Of the 3406 subjects with plaque psoriasis or psoriatic arthritis exposed to TREMFYA, a total of 185 subjects were 65 years or older, and 13 subjects were 75 years or older. No overall differences in safety or effectiveness were observed between older and younger subjects who received TREMFYA. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3) in Full Prescribing Information].* **OVERDOSAGE** In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately. **PATIENT COUNSELING INFORMATION** Advise the patient and/or caregiver to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before starting TREMFYA therapy, and each time the prescription is renewed, as there may be new information they need to know. Hypersensitivity Reactions: Advise patients to discontinue TREMFYA and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions].* Infections: Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions].* Instruction on Injection Technique: Instruct patients or caregivers to perform the first self-injection under the supervision and guidance of a qualified healthcare professional for proper training in subcutaneous injection technique. Instruct patients who are self-administering to inject the full dose of TREMFYA *[see Medication Guide and Instructions for Use].* Instruct patients or caregivers in the technique of proper needle and syringe disposal. Needles and syringes should be disposed of in a puncture-resistant container. Advise patients and caregivers not to reuse needles or syringes. Remind patients if they forget to take their dose of TREMFYA to inject their dose as soon as they remember. They should then take their next dose at the appropriate scheduled time.

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Blaming pharmaceutical companies for what happened is very much in vogue, and no doubt they deserve some of that opprobrium. However, in my view, that is a vast oversimplification of what happened. Although I recognize that physicians are unconsciously influenced by the pharmaceutical industry, I believe those of us who prescribed chronic opioids did so because we thought we were acting in the best interests of our patients.

A Complicated Situation

What follows is my personal recollection of how this complicated situation evolved over several decades. I think it is critical that those trained in the past 10 years or so understand how this story unfolded: "What were they thinking?"

Before and during medical school, I understood that administration of opioids for short courses was appropriate for post-surgical pain or trauma. As a teen, I had several painful kidney surgeries and learned that a shot of meperidine could dramatically relieve severe pain within a few minutes.

My first encounter with chronic use by a patient was in the fall of 1980, during my medical internship. A slight, elderly lady with advanced multiple myeloma was hospitalized under my care; her oncologist had prescribed methadone for severe bone pain. One morning when we could not awaken her, we realized that her methadone levels had accumulated to toxic levels. After we administered naloxone, she woke up, and this sweet little old lady briefly became a raving maniac.

That was around the time that it had become common practice to prescribe long-acting opioids for patients in the final stages of cancer to relieve the pain of expanding lesions in bone and soft tissue. Because life expectancy was limited, physiologic dependency or addiction was not of concern. A letter in the *New England Journal of Medicine* in 1980 carried the headline, "Addiction rare in patients treated with narcotics," and this concept was widely accepted, despite the fact that the assertion was not supported by evidence.[1]

In 1982, I began the clinical year of my rheumatology fellowship and was shocked to find that our revered senior clinician frequently prescribed propoxyphene napsylate with acetaminophen (Darvocet-N) to severe chronic rheumatoid arthritis (RA) patients.

Propoxyphene is a synthetic compound chemically related to methadone approved by U.S. Food & Drug Administration (FDA) in 1957—five years before evidence of efficacy was required in 1962. Of course, this was pre-methotrexate/pre-early administration of disease-modifying anti-rheumatic drugs (DMARDs), and these were patients with extensive damage and deformities.

I observed that his patients did not abuse this analgesic and that it did not have the upper gastrointestinal tract toxicity of aspirin. The similar toxicity of non-steroidal anti-inflammatory drugs (NSAIDs) was not recognized for a few more years. So in the early 1980s, I became comfortable regularly prescribing propoxyphene for RA patients with significant chronic pain, which was almost everyone at the time. Questions about its efficacy existed, but I don't recall problems with tolerance with increasing doses or abuse.

Chronic Non-Malignant Pain

Over time, more attention was given to patients with chronic non-malignant pain. Shortly after I began practice in Wisconsin in 1986, I vividly recall the cover of *Newsweek* calling attention to this problem: "Why does someone need to be dying to have pain relief? Why are doctors not doing more to relieve severe chronic pain, which is so detrimental to the quality of life of these people?"

The issue of the suffering of those with chronic pain became prominent not only in the lay press, but in the medical literature as well. In 1986, the National Institute on Drug Abuse published an article advocating chronic opioid therapy for intractable, non-malignant pain.[2] During my 10 years at Marshfield Clinic in Wisconsin, I managed many chronic pain patients with guidance from pain specialists in the anesthesia department.

Opioid prescribing began to increase appreciably in the 1990s. From 1990 to 1996, prescriptions for opioids increased from 2 million per year to 8 million per year. Many states passed intractable pain acts intended to protect physicians who, in good faith, prescribed chronic opioids for chronic pain.[3]

Pain became *the fifth vital sign*, advocated by the American Pain Society Quality of Care Committee in 1995.[4] The Centers for Medicare and Medicaid Services employed a patient satisfaction survey in determining reimbursement for hospital services that asked: "How often did the hospital or provider do everything in their power to control your pain?" Obviously, if you measure a vital sign and it is abnormal, something must be done to address that. The quality of pain relief became a common topic of patient satisfaction surveys overall. Physicians were criticized for poor patient satisfaction because they refused to prescribe medications for pain.

In 1995, sustained-release oxycodone (OxyContin) was approved, and the FDA-approved labeling stated that iatrogenic addiction was "very rare." The OxyContin tablet was purported to be abuse resistant.

In 2001, the Joint Commission on the Accreditation of Healthcare Organizations introduced standards "as part of a national effort to address the widespread problem of underassessment and undertreatment of pain."[5,6]

In 2010, the FDA took propoxyphene off the market due to arrhythmia concerns, with the recommendation that it be replaced with codeine, morphine or oxycodone.

Key Hypothesis Never Tested

The first big mistake was to assume that the treatment of chronic non-malignant pain would be like that of treating the chronic pain of cancer patients in the last months of their lives.

This hypothesis was not tested; rather, a huge leap was taken in believing the treatment of chronic non-malignant pain would follow the model of treating cancer pain. This was a logical and intuitive assumption, but with our scientific, evidence-based approach to medical practice, we know that a common-sense assumption often does not pass muster when subjected to a prospective, randomized, double-blind clinical trial.

So why was this hypothesis never tested? I suspect two important reasons. Such trials cost millions of dollars and are financially feasible only for companies seeking FDA approval for an investigational medication. Moreover, such trials are typically done over a relatively short term to gain FDA approval, especially for pain relief, not the many years appropriate for a chronic problem. Who would do such a study over many years, and how would it be funded?

This is not meant to excuse the fact that the key hypothesis was not tested, but rather to offer perspective for how difficult and expensive it would have been to perform a study to adequately test the hypothesis that opioid medications would be safe and effective for the treatment of chronic non-malignant pain. In retrospect, phase 4 post-approval studies should have been done to search for safety signals. Instead, the medical community (and the lay public) relied upon a badly flawed assumption.

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A huge leap was taken in believing that the treatment of chronic non-malignant pain would follow the model of treating cancer pain.

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The stage was set for the evolution of an enormous problem, which was not anticipated, based on what we now realize were faulty assumptions, especially in a society in which chronic pain was gaining a high profile, and for which a consensus existed that something needed to be done to relieve the suffering of all these people.

A second huge mistake was to recommend administering analgesic medication in the same manner as for cancer pain.

"Stay ahead of your pain," we advised patients. "Don't wait until you have pain: Take your pain medicine on a schedule, so you always have a good level of medication on board." This might make sense for someone with painful bony metastases, but chronically, this is a formula for the development of tolerance to an opioid medication.

Opioid tolerance is "characterized by a reduced responsiveness to an opioid agonist, such as morphine, and is usually manifest by the need to use increasing doses to achieve the desire effect," and "more than 10-fold escalations of dose in chronic pain management are common," according to Morgan et al.[7] Patients treated this way typically require progressively higher doses of opioid analgesics to achieve pain relief, sometimes reaching doses that suppressed respiration and resulted in fatal overdose.

Standard practice was to advise patients to take their opioid medications in a manner that virtually guaranteed they would develop tolerance, resulting in ever-increasing doses (and toxicity) and physical dependence that produced withdrawal if the dose were decreased or discontinued.

Between 1997 and 2002, morphine, fentanyl and oxycodone prescriptions increased by 73%, 226% and 40%, respectively.[8] Around 1999 it was recognized that overdose deaths from prescription opioids were increasing, and of course, this trend has continued for years.

Opioid Crisis

The opioid crisis is a very complicated phenomenon. The Centers for Disease Control and Prevention (CDC) divides it into three general phases: the first from 1990–99, dominated by prescription opioids; the second from 2000–13, dominated by heroin; and the third from 2013 on, dominated by fentanyl.[9] From the standpoint of physician prescribing, the first phase dominated by prescription opioids is of the most interest to me.

A third major problem has been the lack of understanding of addiction and which persons have the greatest risk of developing addiction.

Dependence vs. Addiction

Opioid dependence develops when patients have clinical withdrawal as the dose is reduced or withheld. This is distinct from addiction, which is the compulsive, harmful, sometimes illegal use of a chemical substance.

A common misconception exists that anyone can become addicted by taking opioids. It is true that patients taking opioids for over three months do have an increased risk of developing addiction.[10] Observational studies show that "of patients who receive a single opioid prescription in the emergency department, after surgery or at the dentist's office, 1% to 6% end up using opioids for at least 12 months or being diagnosed with opioid use disorder."[11]

The potential to develop addiction is neurochemical. Addiction develops when the limbic system (or the *lizard brain*) *hijacks the brain's frontal lobe*. In the case of opioids (or alcohol, or other substances), the lizard brain derives such intense pleasure from the opioid stimulation that it demands more input, overriding the frontal lobe's restraint. This is not a conscious act: the primitive brain takes over, and opioid use becomes compulsive and unrestrained.[12]

A prevailing assumption is that taking prescription opioids leads to heroin addiction. An analysis by the National Institute on Drug Abuse, National Institutes of Health and the FDA notes, "Available data indicate that the *nonmedical* [emphasis mine] use of prescription opioids is a strong risk factor for heroin use"; however, "heroin use among people who use prescription opioids for medical reasons is rare, and the transition to heroin use appears to occur at a low rate."[13]

I do not make this point to excuse those with chemical dependency. We are all ultimately responsible for our actions, and if an addicted individual develops insight into their problem, it requires hard work and making good decisions to recover. The point is that only a minority of people are preprogrammed to develop addiction.[20,21] It is often stated that many individuals who become addicted to illicit drugs start with prescription drugs, but it does not logically follow that *all* persons who take prescription opioids are at risk of becoming addicted.

So how does one know in advance that a patient is prone to develop addiction, that their brains are primed for addiction? Some situations are obvious, but in many cases it is not possible to know in advance, and therein lies the dilemma for the prescribing physician. One solution is to have, at the outset, a *pain contract*, which stipulates the rules for receiving opioids (or other controlled medications), and the understanding that violating the contract means the end of more prescribing. (In my experience, second chances have a very predictable negative outcome.)

Although many patients have abused opioids, it is wrong to categorically label all patients taking chronic opioids as *addicted*.

Finally, I think it is a mistake that patients doing well on "acceptable," stable doses of opioids have, in many cases, had these medications withdrawn entirely.[13]

The 2016 CDC Guideline for Prescribing Opioids for Chronic Pain was misconstrued by insurance companies and physicians (myself included) as a mandate to aggressively reduce opioid doses.[10] The U.S. Department of Health and Human Services issued subsequent clarification: "More judicious opioid analgesic prescribing can benefit individual patients as well as public health when opioid analgesic use is limited to situations where benefits of opioids are likely to outweigh risks."[15]

Nonetheless, it has become common practice for doctors assuming care of these patients to withdraw them completely from opioids. "The fact that someone has been taking opioids for years does not mean the person has opioid use disorder, but many people make that stigma-driven assumption."[16]

The CDC and the FDA have described legacy patients who were started on chronic opioids years ago when the treatment was considered medically appropriate. How should these patients be treated when pain clinics close, or their physicians relocate or retire?[17] Finding fault with patients for taking medications prescribed by their physicians is not appropriate; nor is regarding every patient taking opioids an addict.

Thoughtful opinion pieces have appeared in major journals taking issue with "an all-or-nothing approach to pain management." A perspective piece in the *New England Journal of Medicine* opined that "as the pendulum swings from liberal opioid prescribing to a more rational, measured, and safer approach, we can strive to ensure that it doesn't swing too far, leaving patients suffering as the result of injudicious policies."[18]

Many negative outcomes have occurred as a result of tapering and discontinuing opioid therapy for chronic pain.

We have seen such drastic change before, when post-menopausal estrogen therapy was dramatically curtailed after data showed that continuous Prempro therapy increased the risk for breast cancer. Almost overnight, estrogen replacement therapy was virtually abandoned, even regimens for which an increase in breast cancer had not been demonstrated.

Forty-two years after receiving my medical degree, it seems to me that the medical community finds it difficult to recognize Aristotle's maxim that "the virtue in all things lies in a mean between two extremes." Very few therapeutic decisions are fundamentally binary.

Lessons Learned

I do not claim to have the answer to this conundrum, but all physicians can learn very important lessons from this experience. We need to be cautious about adopting therapies that *make sense* because, in the fullness of time, we may recognize that such a decision was misguided. And we need to be humble in judging previous practices made in good faith by physicians who thought they were doing the right thing for their patients.

I have been in medicine long enough to see the error of such ideas as "don't start treatment of rheumatoid arthritis until it has been present for at least a year, because it might go away, and the treatments are very toxic." In many cases, what we consider standard of care in 2022 may be regarded with derision decades later. **R**

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PSORIATIC ARTHRITIS
THE OBESE PATIENT

A complex relationship

■ BY LINDA KOSSOFF

'If obesity affects your patient, you need to look around & see what resources you can use to build a team to address it.'

—M. Elaine Husni, MD, MPH

The National Psoriasis Foundation estimates that more than 8 million people in the U.S. suffer from psoriasis and that approximately 30% of those individuals develop psoriatic arthritis (PsA).[1] Given these statistics, roughly 2.4 million people in the country are likely affected by PsA. Moreover, patients with this systemic condition carry a higher-than-average burden of cardiometabolic comorbidities, such as diabetes, hypertension, cardiovascular disease—and obesity.

"Obesity is one of the stronger risk factors for development of psoriatic arthritis, along with severe psoriasis, history of joint trauma, family history and inflammatory bowel disease," says rheumatologist Alexis Ogdie, MD, MSCE, associate professor of medicine and epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, and director of the Penn Psoriatic Arthritis and Spondyloarthritis Program.

Dr. Ogdie estimates that approximately 50% of patients with PsA in the U.S. have a body mass index (BMI) of more than 30, a percentage exceeding that of the entire nation's general population by just 9%, according to currently available statistics from the Centers for Disease Control and Prevention.[2] The overall trend toward a more obese populace is expected to continue, and, thus, rheumatologists can expect the number of patients they see with PsA who also are obese to rise as well.

The relationship between PsA and obesity is complex and possibly bidirectional in nature. It has been theorized that the chronic systemic inflammation that characterizes obesity is not only caused by the excess weight but may be a risk factor for it.[3] This is one of many reasons treatment management for patients affected by both PsA and obesity is particularly challenging for the rheumatologists and rheumatology professionals who work with them. Many are exploring new ways to approach and care for these patients.

The Weight Factor

Given the progressive nature of PsA, the earlier the disease can be diagnosed the better the long-term treatment outcome, says Dr. Ogdie. However, any diagnosis of PsA can take time, as undiagnosed patients generally first go to their primary care doctor, who might find inflammatory conditions that point to PsA. "Having uveitis or inflammatory bowel disease, for example, might elevate the likelihood that the patient's joint complaints are psoriatic arthritis, and speed up diagnosis," Dr. Ogdie notes.

However, an obese patient, particularly one without any of these telltale inflammatory conditions, can be especially difficult to diagnose, according to Dr. Ogdie. "People with obesity have a higher prevalence of osteoarthritis, so this can be hard to separate out—are these symptoms of osteoarthritis, is this mechanical in general, or is it psoriatic arthritis?" she says. "Patients with obesity have a higher prevalence of fibromyalgia and that's also sometimes difficult to distinguish from PsA."

Weight also factors in when considering the patient's potential responsiveness to drug therapy. M. Elaine Husni, MD, MPH, is a rheumatologist at the Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, and a researcher at its Lerner Research Institute. "If we focus on psoriatic arthritis patients, there are a lot of disease-modifying anti-rheumatic drugs [DMARDs] available," she says. "In general, we know that certain medications don't work as well when you have an elevated BMI, and that outcomes for surgery and other procedures are not as positive when patients are overweight or obese. For example, with TNF [tumor necrosis factor] inhibitors, there is research showing that patients with an elevated BMI will take a longer time to reach minimal disease activity when compared to patients with a normal BMI. We also know that if a patient reduces their elevated BMI down to a normal one, that the drugs work better."[4,5]

In addition to maximizing the effectiveness of medications, weight reduction can help patients with PsA in other ways. "All of your cardiometabolic comorbidities may escalate when you have obesity, and, because psoriatic arthritis has a higher burden to begin with, due in part to an ongoing low-grade inflammatory state, the higher BMI just adds to this issue," explains Dr. Husni. "We consider weight to be a modifiable risk factor and that's why we really want to help change this factor."

Broaching the Subject

Once a diagnosis of PsA has been reached, the issue of obesity becomes more central to the conversation of what to do next. This can be a difficult and sometimes delicate aspect of the patient's care. No one goes to a doctor to receive a lecture on weight loss. For people struggling with obesity, such conversations are often painful and anything but helpful because they have likely heard it all before. Both Dr. Ogdie and Dr. Husni emphasize the importance of fostering a safe, nonjudgmental relationship with these patients. For the first visit, that means providing as much objective information as possible before venturing into more sensitive areas.

After an initial assessment to identify the patient's comorbidities and health history, a physical exam to understand what is happening with the joints, and a discussion of appropriate medications to address symptoms, Dr. Ogdie talks to obese patients about their cardiovascular risk based on their lipid profile.

Dr. Ogdie then proceeds to a discussion of body mechanics. "We can take care of joint inflammation, but that doesn't address how well their body is moving," she says, noting that her patients are usually referred to physical therapy for that. From there, she moves on to talking about depression or anxiety. Patients with psoriasis and psoriatic

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arthritis have an elevated risk of mood disorders, which increases the likelihood of unhealthy lifestyle habits.[6]

"Then at some point, depending on how the patient is responding, I bring up their weight," says Dr. Ogdie. "If they are interested in hearing more, I might talk about how healthy diets, such as cutting out simple carbs, can help psoriatic arthritis. I might bring up the patient's BMI and make it clinical, saying that we know that patients with a BMI of over 30 don't respond as well to therapy and that if you reduce body weight by 5% to 10%, you'll likely significantly improve your response to therapy."

How far this conversation goes, however, is up to the patient. "The last thing you want is to overwhelm your patients on the first visit, when they are dealing with a diagnosis of a chronic illness," stresses Dr. Husni. "Obviously, they're there to hear about the illness itself and treatments for psoriatic arthritis. So instead of listing all the advice right off the bat, I like to choose which associated issue to discuss at a particular visit. If it is time to talk about weight management, *I ask for permission to talk about their weight*. Some patients say, 'Yeah, bring it on, what do you know about obesity, what can I do?' and others say, 'You know, I've heard it all. I'm really trying, and I don't want to talk about it right now.' In that case, I'll say, 'Oh, that's okay, we don't have to address this at this visit.'

"If you simply list all the things someone needs to do while getting their arthritis treated with anti-TNF therapy—such as lose weight, exercise three times a week, raise their heart rate 20 minutes a day and eat a well-balanced diet—they're just not going to do it."

Physical activity can be harder for obese people, and those who also have PsA are especially wary about exercise because they fear it might hurt their joints and/or worsen their symptoms—unfounded yet common fears, according to Dr. Ogdie. These patients may need extra reassurance and guidance from their medical team to feel safe about exercising. It can also be helpful to remind patients that additional weight gain is more likely when they are not physically active.

Treatment Strategies

The standard treatment approach for all patients with PsA may not be as effective in a patient with a BMI above 30. Although studies show the obese body may not respond as well to medications typically used to address inflammation as non-obese bodies do, the reasons for this are still being explored.

"We do know that adipocytes produce inflammatory cytokines, which may increase the obese patient's joint inflammation," says Dr. Ogdie. "In addition, giving every patient with PsA the same 40 mg dose of adalimumab regardless of their weight really doesn't make sense, but that's what the original study suggests. It's just one dose for everybody. So patients not getting the appropriate dose for their body weight may also play a role."[7]

Additional challenges to treatment include "the typical lifestyle habits that go along with having a chronic disease," says Dr. Husni. These may include poor sleep, inability to exercise and a worsened response to stress, all of which can be more pronounced when dealing with a chronic illness.

"Given the evidence now, we have shifted our attitude; improvements in our lifestyle behaviors are important and not likely something that is optional," Dr. Husni says. "We encourage our patients to discuss how to modify their lifestyle behaviors when they have a chronic illness. These 'wellness strategies' may not be a luxury, but rather, a critical adjunctive concern that needs to be addressed. They are just as important as treating the disease."

Stressing that lifestyle changes are intertwined with psychosocial health, she advocates for a whole-patient approach, which she feels is especially key for obese patients, whose condition is frequently misunderstood.

"It's easy for us to dismiss people who are obese and think they don't care about themselves or that they choose not to change their habits," Dr. Husni says. "However, there are different stages of treating obesity now. We have a greater understanding of the hormones related to obesity, such as ghrelin and leptin, and how they can become dysregulated to result in a higher weight set point."

At the Cleveland Clinic, Dr. Husni can refer patients with more urgent weight-related needs to the clinic's Endocrine and Metabolic Institute for care. Dr. Ogdie reports that Penn is currently running a diet trial for patients with a BMI of 25–40. The focus, she explains, is on lifestyle changes over monitoring weight, although both are in the mix. She has referred her patients to the study.

Dietary guidance, although helpful, should be just part of a broader treatment plan for obese patients with PsA, say both rheumatologists. "It's important that we understand all the different comorbidities of psoriatic arthritis, obesity being one of them. And if obesity affects your patient, you need to look around and see what resources you can use to build a team to address it," says Dr. Husni.

In this regard, she acknowledges the benefit of practicing rheumatology in a co-management clinic. "Part of our job is to collect a patient's profile of risk factors. Then we can build our team (bring in other specialists) to help address these factors," she explains. "I have dermatologists, cardiologists and psychologists. I have a smoking cessation program. We see these patients over a lifetime, and we help them prioritize their health issues. So if obesity needs to be prioritized because they're cycling through a lot of medications and not improving, they may consider getting to a more normal BMI. If a patient is in a low disease activity state with stable exams, labs and imaging, I may prioritize the psychosocial aspects for that patient rather than escalating DMARDs. It's just not one size fits all."

Therein lies another challenge. How many patients in the U.S. have access to a team of specialists to help resolve a complex and multifaceted problem like psoriatic arthritis with obesity? How many rheumatologists have the resources to gather a team, much less the time to oversee team-based care?

"I have the luxury of a full hour for a new patient visit and then 20 minutes or so for a return patient visit, which not everyone has," acknowledges Dr. Ogdie. Still, it is not enough. Penn is starting a single-arm trial funded by a grant from the Rheumatology Research Foundation testing a new model that, she says, "basically takes it out of the doctor's hands" by having a nurse or nurse practitioner handle regular visits. At Dr. Ogdie's office, a nurse practitioner takes a full day of telemedicine calls for existing patient check-ins once a week. Education resources for the patient, such as handouts, also carry some of the load.

Finally, what does the current U.S. health system allow? "It would be great for people to understand the costs of obesity in psoriatic arthritis because insurance companies should really be thinking about covering those costs," says Dr. Ogdie. "As it is, it's hard to get people to physical therapy because of the high copay, and patients often can't get coverage for a nutritionist unless they have cancer. They can't get the mental healthcare they need because our current health system isn't set up to help. Those are the kinds of things that need to change to help these patients." R

Linda Kossoff is a medical writer based in Los Angeles.

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For moderate to severe rheumatoid arthritis (RA) in adult TNFi-IR patients[1]

RINVOQ® upadacitinib

DEFY EXPECTATIONS

CHALLENGE TREATMENT GOALS IN RA WITH A ONCE-DAILY ORAL JAK INHIBITOR

RINVOQ met ALL primary (ACR20 or ACR50 at Week 12 or 14) and ranked secondary endpoints across RA clinical trials.[1-3]

INDICATIONS[1]

RINVOQ is indicated for the treatment of:

- **Moderately to severely active rheumatoid arthritis** in adults who have had an inadequate response or intolerance to one or more TNF blockers.
- **Active psoriatic arthritis** in adults who have had an inadequate response or intolerance to one or more TNF blockers.
- **Active ankylosing spondylitis** in adults who have had an inadequate response or intolerance to one or more TNF blockers.

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

- **Refractory, moderate to severe atopic dermatitis** in adults and pediatric patients 12 years of age and older 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.

- **Moderately to severely active ulcerative colitis** in adults 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 other potent immunosuppressants such as azathioprine and cyclosporine.

SAFETY CONSIDERATIONS[1]

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

ACR=American College of Rheumatology; AD=atopic dermatitis; AE=adverse event; AS=ankylosing spondylitis; bDMARD=biologic DMARD; csDMARD=conventional synthetic DMARD; DAS28-CRP=28 joint Disease Activity Score using C-reactive protein; DMARD=disease-modifying antirheumatic drug; IR=intolerance or inadequate response; JAK=Janus kinase; mTSS=modified total Sharp score; MTX=methotrexate; PsA=psoriatic arthritis; TNFi=tumor necrosis factor inhibitor; UC=ulcerative colitis.

LONG-TERM REMISSION AND LOW DISEASE ACTIVITY DATA observed **up to 84 weeks** with or without MTX[1,3-6]

- DAS28-CRP<2.6* and DAS28-CRP≤3.2 evaluated at Week 12 or 14, with response rates from 60 to 84 weeks (in SELECT-BEYOND and SELECT-MONOTHERAPY, respectively)

***Clinical remission does not mean drug-free remission or complete absence of disease activity.**

WELL-STUDIED SAFETY DATA FROM 18 CLINICAL TRIALS ACROSS 5 INDICATIONS

AEs observed in long-term analysis with ~5.5 years maximum exposure beginning in RA (~3.5 years median) to RINVOQ 15 mg as of 6/30/21[7,a,b]

- 18 clinical trials establishing a breadth of experience across 5 indications[1,8-10,c]
- >10,500 patients in global clinical trials across US-approved indications, including pediatrics 12+ years in AD[1,8,9,11,12,d]
- >18,500 patient-years of exposure to RINVOQ 15 mg or 30 mg[8,12-16,d,e]

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[a]SELECT-EARLY (RA-I; MTX-naïve) [primary endpoint at Week 12: ACR50 response vs MTX, select ranked secondary endpoint at Week 24: ΔmTSS vs MTX]; SELECT-MONOTHERAPY (RA-II; MTX-IR) [primary endpoint at Week 14: ACR20 response vs MTX, select ranked secondary endpoints at Week 14: DAS28-CRP<2.6 vs MTX, DAS28-CRP≤3.2 vs MTX]; SELECT-NEXT (RA-III; csDMARD-IR) [RINVOQ + csDMARD; primary endpoint at Week 12: ACR20 response vs placebo + csDMARD]; SELECT-COMPARE (RA-IV; MTX-IR) [RINVOQ + MTX; primary endpoint at Week 12: ACR20 response vs placebo + MTX, select ranked secondary endpoint at Week 26: ΔmTSS vs placebo + MTX]; SELECT-BEYOND (RA-V; bDMARD-IR) [RINVOQ + csDMARD; primary endpoint at Week 12: ACR20 response vs placebo + csDMARD, select ranked secondary endpoint at Week 12: DAS28-CRP≤3.2 vs placebo + csDMARD].[1,2]
[b]SELECT-CHOICE (bDMARD-IR) [RINVOQ + csDMARDs; primary endpoint at Week 12: ΔDAS28-CRP (noninferiority) vs active comparator + csDMARDs].[17]
[c]Includes SELECT-EARLY, SELECT-MONOTHERAPY, SELECT-NEXT, SELECT-COMPARE, SELECT-BEYOND, and SELECT-CHOICE for RA; SELECT-PsA 1 and SELECT-PsA 2 for PsA; SELECT-AXIS 1 and SELECT-AXIS 2 for AS; Measure Up 1, Measure Up 2, AD Up, and Heads Up for AD; U-ACHIEVE Induction, U-ACCOMPLISH Induction, U-ACHIEVE Maintenance, and the long-term extension study for UC.[1,8-10]
[d]RA: RINVOQ 15 mg, upadacitinib 30 mg; PsA: RINVOQ 15 mg, upadacitinib 30 mg; AS: RINVOQ 15 mg; AD: RINVOQ 15 mg, RINVOQ 30 mg; UC: RINVOQ 15 mg, 30 mg, and 45 mg. RINVOQ 15 mg is the approved dose in RA, PsA, and AS; RINVOQ 15 mg and 30 mg are the approved doses in AD; RINVOQ 15 mg, 30 mg, and 45 mg are the approved doses in UC.[1,8,9,13,15]
[e]Includes 12,259.5 patient-years in RA trials, 2504.6 patient-years in PsA trials as of 06/2020, 577.3 patient-years in AS trials, 2787.6 patient-years in AD trials as of 11/2020, and 381.1 patient-years in UC trials.[8,12-16]

SAFETY CONSIDERATIONS (CONTINUED)[1]

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

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

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

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

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

Other Serious Adverse Reactions: Hypersensitivity Reactions (anaphylaxis and angioedema), Gastrointestinal Perforations, Laboratory Abnormalities (neutropenia, lymphopenia, anemia, lipid elevations, liver enzyme elevations), and Embryo-Fetal Toxicity.

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

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

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IMPORTANT SAFETY INFORMATION FOR RINVOQ® (UPADACITINIB)[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.

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.

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.

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

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

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

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

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 228 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.

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, and Ankylosing Spondylitis

The safety and effectiveness of RINVOQ in pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis 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.

Renal Impairment

For patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, 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, or ankylosing spondylitis.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, and ankylosing spondylitis, 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.

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Ref: 20071734 Revised: April 2022

LAB-7083 **MASTER**

US-RNQR-220617

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The 2022 ARP President's & Merit Awards

13 ARP members honored

■ **BY PATRICE FUSILLO**

During ACR Convergence 2022 in early November, the ACR and the ARP honored a group of distinguished individuals who have made significant contributions to rheumatology research, education and patient care. This month, *The Rheumatologist* profiles the recipients of the ARP President's and Merit Awards.

ARP PRESIDENT'S AWARDS

The ARP president can choose to honor ACR/ARP members or teams performing outstanding service within the present year to advance the goals, ideals and standards of the ARP. This year, ARP President Barbara A. Slusher, PA-C, MSW, announced two recipients of the President's Award, **Kaleb Michaud, PhD**, and **Brit Donaldson, PA-C, MMS**.

Kaleb Michaud, PhD, is a professor in the Division of Rheumatology and Immunology at the University of Nebraska Medical Center, Omaha.

Dr. Michaud's experiences as a patient with a rheumatic disease have powered his passion and dedication to improving rheumatology and patient outcomes. He serves as director of FORWARD—the National Databank for Rheumatic Diseases, a long-term, open-cohort observational study with over 50,000 enrolled participants. He leads the University of Nebraska Medical Center Rheumatoid Arthritis Investigational Network (RAIN) clinical database and collaborates with the Veterans Affairs Rheumatoid Arthritis (VARA) registry, the Rheumatology Informatics System for Effectiveness (RISE) registry and others.

A scholar in pharmacoepidemiology, health informatics and cost-effectiveness, Dr. Michaud prioritizes mentoring and volunteering to grow the next generation of healers, scientists and difference-makers. Some of his current projects include disease-modifying anti-rheumatic drug (DMARD) adherence, mortality in rheumatic diseases, rheumatoid arthritis activity measures and smartphone-detected health outcomes.

Within the University of Nebraska Medical Center, Dr. Michaud is the director of the rheumatology fellowship research program, chair of the Clinical Research Center pilot grant review committee and leader of the Great Plains Institutional Development Award and Clinical and Translational Research (IDeA-CTR) Mentor Training Facilitator Team. He is dedicated to conducting research that improves care for those living with rheumatic diseases.

Dr. Michaud is an active, 20-year volunteer in the ARP and the ACR.

"I am truly honored to receive this award. My volunteer journey in the ARP has been to ultimately make our rheum patients' lives better through research, mentoring and having an organization responsive and responsible for our professionals' needs," says Dr. Michaud. "Being recognized like this along the way comes as a wonderful surprise!"

Brit Donaldson, PA-C, MMS, is a physician assistant (PA) in pediatric rheumatology at Atrium Health Wake Forest Baptist, Winston-Salem, N.C. Prior to becoming a PA, she worked in a general pediatrics clinic. She became interested in rheumatology early in her training and started her PA career in adult rheumatology, but then decided to switch to pediatric rheumatology. Ms. Donaldson enjoys working with children with rheumatic conditions and their families and hopes to improve patients' self-efficacy and help them feel supported through their experiences living with chronic conditions.

Outside her clinical duties, Ms. Donaldson enjoys precepting and teaching. She collaborates with the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry and other research projects with her team and volunteers with the ACR/ARP on the Pediatric Rheumatology Symposium (PRSYM) Planning Committee and the Workforce Solutions Committee. Ms. Donaldson was a faculty moderator for The Training Rheum earlier this year.

Some of her professional goals are to increase rheumatology awareness and education for medical trainees and to improve training for rheumatology professionals to help ensure a sustainable workforce and support better access to care for patients.

"I am honored to receive this award. I have been extremely fortunate to have an outstanding team and supportive mentors and am very thankful for the resources the ACR provides to members and patients," says Ms. Donaldson. "It has been very rewarding to volunteer with the ARP/ACR and to help support training for advanced practice providers in rheumatology. I am excited for our field and allied health professionals' roles in improving patient access and care."

When she is not at work, Ms. Donaldson enjoys road and gravel cycling, mountain biking, hiking, camping, reading and traveling.

ARP MERIT AWARDS

The ARP Merit Awards recognize outstanding contributions to the field of rheumatology.

ARP Master Awards

The ARP's highest honor—the Master Award—went to two ARP members in 2022 for their outstanding contributions to the field of rheumatology: **Janet L. Poole, PhD, OTR/L, FAOTA,** professor, University of New Mexico, Albuquerque, and **Jan K. Richardson, PT, PhD, OCS, FAPTA,** chief medical officer for Medical Outcome Indicators, Washington, Pa.

Janet L. Poole, PhD, OTR/L, FAOTA, is a professor, division chief and director of the Occupational Therapy Graduate Program in the Department of Pediatrics, School of Medicine at the University of New Mexico.

Dr. Poole began working with people with arthritis very early in her career as an occupational therapist at the University of Virginia, Charlottesville. Her clinical interest in, and dedication to, people with scleroderma was fostered by Thomas Medsger, MD, and Virginia Steen, MD. She has also been inspired and supported by other rheumatologists to remain committed to people with scleroderma.

As an occupational therapist, Dr. Poole is invested in the impact of scleroderma on daily life activities. She teaches rheumatology to occupational therapy students and has involved them in research projects. Dr. Poole routinely speaks at meetings of the American Occupational Therapy Association (AOTA) to educate therapists on the role of occupational therapy in scleroderma and other rheumatic conditions and was named a fellow of the AOTA and inducted into the Academy of Research for the American Occupational Therapy Foundation.

Dr. Poole has a history of productive research projects with, and funding from, the Patient-Centered Outcomes Research Institute (PCORI), the Rheumatology Research Foundation, the National Institute of Nursing Research (NINR) and the National Scleroderma Foundation, resulting in numerous publications and national and international presentations. She designed an internet-based, self-management program (Taking Charge of Systemic Sclerosis [TOSS]; **https://www.selfmanagescleroderma.com**) and developed educational materials on hand and face exercises, management of fatigue and a program to keep people with scleroderma in the workforce. She has tried to ensure that these programs are easily accessible to patients and shares information at patient conferences. In 2011, Dr. Poole was recognized by the Scleroderma Foundation with the National Volunteer of the Year Award.

An active member of the ARP since 1984, Dr. Poole has served on numerous ARP and ACR committees as both a member and chair. Dr. Poole was the 2020 ARP president and served in officer roles as secretary, president-elect and immediate past president. Dr. Poole delivered the Distinguished Lecture at the 2018 ACR Annual Meeting and received the ARP Distinguished Educator Award in 2014 and the ARP Distinguished Clinician Award in 2012. She routinely presents at the ACR's annual meetings.

Dr. Poole also collaborates with patients, patient groups, professional organizations and rheumatology professionals from Canada and Europe to develop educational materials and guidelines for non-pharmacological interventions for people with scleroderma. Dr. Poole feels the ARP/ACR has provided networking and leadership opportunities that have led to a successful and enjoyable career in rheumatology.

Dr. Poole received her Bachelor of Science in occupational therapy from Colorado State University, her Master of Arts from the University of North Carolina, Chapel Hill, and her doctorate from the University of Pittsburgh.

"I am so honored and humbled to receive the ARP Master Award. I am in awe of those who have received this designation in the past," says Dr. Poole. "I have been a member of ARP for over 30 years. During this time, the ARP has afforded me so many opportunities, including networking with experts in scleroderma and other rheumatic diseases and people with scleroderma, and leadership opportunities, including being the president of the ARP in 2020. I have grown professionally, and value the long-term friendships and collaborations developed through volunteering on many different interprofessional committees and task forces."

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Jan K. Richardson, PT, PhD, OCS, FAPTA, is chief medical officer for Medical Outcome Indicators (MOI) and professor emeritus, School of Medicine, Duke University, Durham, N.C. Dr. Richardson has also served as chief clinical officer for Universal SmartComp, Washington, Pa., as well as a professor of community and family medicine, founding chief of the Doctor of Physical Therapy (DPT) program and executive director of the Department of Physical Therapy and Occupational Therapy at Duke University Medical Center.

She also served as the founding chair/professor of the DPT program, and executive director and chief executive officer for the Institute for Health Care and Research at Slippery Rock University, Pennsylvania. She has been in consulting and advisory positions with One Source, a board member of the U.S. Bone and Joint Institute representing the ACR, and serves as an expert witness. Dr. Richardson earned a doctorate and a Master of Science from the University of Pittsburgh, her post-graduate physical therapy education from the University of Pennsylvania, Philadelphia, and a Bachelor of Science from Pennsylvania State University, State College.

Active in the American Physical Therapy Association (APTA) at both the national and local levels, Dr. Richardson was APTA president, served as the U.S. delegate to the World Confederation of Physical Therapy, was a member of the executive committee of the APTA Board of Directors, and served as chair of the national TriAlliance of the APTA/American Occupational Therapy Association (AOTA)/ American Speech-Language-Hearing Association (ASHA) and the American Board of Physical Therapy Specialties (ABPTS) Task Force for Specialization.

Dr. Richardson has also served as the president of the ARP and on the executive committee of the ACR. Additionally, she initiated the physical therapy component of the Global Health Outreach Initiative at Duke University, traveling to India and Kuwait in the process. She served as a volunteer with a healthcare system in western Pennsylvania and with the Western Pennsylvania Hospital Council.

Dr. Richardson has received numerous awards and honors throughout her career, including the Catherine Worthingham Fellow Award (APTA), Lucy Blair Service Award (APTA) and the Stanley Paris Award (AOPTA/APTA) and was selected nationally as an Executive Leadership in Academic Medicine Fellow (ELAM).

With her co-investigator, Chad Cook, Dr. Richardson pioneered early work in the establishment of valid and reliable scales for pain and disability. Further areas of research included validation of an item bank in community-dwelling survivors of stroke, looking into the meta-analyses of human immunodeficiency virus (HIV) treatments supported by biomedical oncology, and investigation into the use of physical therapy in patients hospitalized with a diagnosis of generalized weakness.

"I am honored to receive the Master designation from the ARP," says Dr. Richardson. "The ARP has given me many opportunities throughout my career to serve in leadership positions and to contribute to the vision and goals of the ACR Association. The relationships that I have developed with colleagues have strengthened my abilities to enhance practice, advance research and foster education for the patients we serve and the profession of rheumatology."

Lifetime Achievement Award

Among the ARP's highest honors is the Lifetime Achievement Award, which is presented to a current or past member who has made meaningful and lasting contributions to the field of rheumatology. This year's award recipient is **Marian T. Hannan, MPH, DSc,** professor of medicine at Harvard Medical School, Boston, and a senior scientist and co-director of the Musculoskeletal Research Center at the Hinda & Arthur Marcus Institute for Aging Research at Hebrew Senior Life, Boston, as well as a former president of ARP (then known as ARHP) in 1998–99.

Dr. Hannan has been an ARP member since 1988 and has enjoyed parallel growth of her career along with growth within the ARP.

"I am incredibly honored to receive the ARP Lifetime Achievement Award, especially as the ARP is my professional home and a community chockful of incredible, dedicated people," says Dr. Hannan.

"I have spent a 'scientific lifetime' in the ARP/ACR, presenting talks, helping on committees, serving as editor of *Arthritis Care & Research* and giving my all to our organization. Rheumatology is a team sport, and I am fully grateful to every player, coach, talent scout, advisor and sponsor (thank you RRF [Rheumatology Research Foundation]!) for the honor of our play over the years."

For a decade earlier in her career, Dr. Hannan worked with the Boston University Arthritis Center, and over the past 25 years she has conducted research at the Marcus Institute.

Dr. Hannan conducts research focused on osteoarthritis, foot biomechanics, fractures and osteoporosis. She is widely published, with more than 200 articles presented in over 50 scientific journals in the medical field, including *Arthritis Care & Research, The New England Journal of Medicine, Arthritis & Rheumatology* and the *Journal of Bone & Mineral Research.*

She has been the principal investigator on a number of National Institutes of Health (NIH) grants and has had continuous NIH grant funding since 1996. She collaborates closely with investigators in Boston, using the combined expertise of bioengineers, rheumatologists, nutritional epidemiologists, geneticists, molecular biologists and statisticians to quantify risk factors contributing to musculoskeletal diseases. Dr. Hannan reviews grant applications nationally and internationally.

At Harvard Medical School, Dr. Hannan teaches clinical epidemiology and population health to first-year medical students. She also lectures in the school's geriatrics fellowship program. Dr. Hannan is the course director of the Frailty Course at Harvard School of Public Health. Her mentoring of young investigators includes many scientists and medical fellows in the Boston area, as well as early stage investigators across the U.S. and Canada through the U.S. Bone & Joint Initiative's Young Investigator Initiative. One of her great joys is mentoring young researchers as they grow their careers. She is an award-winning mentor and enjoys contributing to the next generation of innovative medical research.

Dr. Hannan received her undergraduate degree at the University of California, Berkeley, a Master of Public Health at Yale University School of Medicine, New Haven, Conn., and a doctorate in epidemiology at Boston University School of Medicine.

"We all stand on the shoulders of giants in our field," Dr. Hannan notes, and she offers her heartfelt thanks to ARP/ACR members from whom she has learned so much about science and received helpful feedback. Most importantly, she applauds the combined efforts within the ACR that have brought rheumatology research forward.

Addie Thomas Service Award

The 2022 Addie Thomas Service Award is presented to an ARP member in honor of the Association's first president and recognizes active volunteers in arthritis-related activities. This year's recipient is **Charles G. Helmick, MD**.

Dr. Helmick graduated in 1972 from the University of Michigan, Ann Arbor, and in 1976 from the Johns Hopkins School of Medicine, Baltimore. After training in internal medicine, he joined the Epidemic Intelligence Service (the disease detective training program) at the Centers for Disease Control and Prevention (CDC). There he worked on exotic infectious diseases in international settings before switching his focus to chronic diseases as the bigger health problem. Dr. Helmick worked part time in the Atlanta VA Rheumatology Clinic for 12 years, where he learned more about rheumatic diseases firsthand. He retired as a captain in the U.S. Public Health Service in 2009 and from the civil service with the CDC in 2021.

When Dr. Helmick's effort to address aging-related problems got little traction at the CDC in the early 1990s, he switched his focus to the most salable of those public health problems—arthritis. Working with former ARHP President Teresa Brady, the Arthritis Foundation, the ACR/ARHP and other partners, he helped develop the National Arthritis Action Plan: A Public Health Strategy. This document provided support for Congress' first funding for the CDC's Arthritis Program in 1999.

Since then, the CDC Arthritis Program has worked to provide basic and more advanced national-, state- and county-level measures of the public health impact of arthritis and other rheumatic conditions and to raise their visibility as health problems. The program also worked to develop and promote evidence-based but underused interventions, such as self-management education and physical activity, reaching hundreds of thousands of adults with arthritis.

He also worked to do the same for lupus by establishing registries in 2003 across the U.S. Because pain is a key symptom of these conditions, later in his career he began to work with national organizations to address pain as a major public health issue and arthritis as a major cause of pain. Arthritis and (separately) pain are now addressed in key national planning documents, such as the U.S. Department of Health and Human Services' Healthy People objectives.

Dr. Helmick has been a member of the ARP since 1996, worked closely with many ARP leaders over the years and received multiple ARP awards. He was a member of the *Arthritis Care & Research* Editorial Board and continues as a long-time contributor to the journal. He worked to make the ARP the national home for public health science and intervention activities that address arthritis and other rheumatic conditions.

Dr. Helmick says, "The ARP is the perfect place to work on bridging the clinical-community gap in health and to achieve what we all want—better health and quality of life for people affected by arthritis and other rheumatic conditions. The population burden and individual impact of arthritis and rheumatic conditions is under-recognized in the United States. For me this award helps recognize those of us who have worked to change that by focusing on the big picture and communicating it more widely."

Ann Kunkel Advocacy Award

The 2022 Ann Kunkel Advocacy Award, recognizing an ARP member who has provided extraordinary service in advocating for patients with arthritis and rheumatic diseases or for health professionals in rheumatology, was presented to **Sue MacQueen, PT, BScPT, ACPAC**.

Ms. MacQueen graduated from the University of Western Ontario, London, in 1980 with a BScPT degree and worked at Grand River Hospital, Kitchener, Ontario, as staff physiotherapist until 1988 when she started working with the Arthritis Society's Arthritis Rehabilitation and Education Program (AREP) in Kitchener.

She has been active in the assessment and management of people living with arthritis and has developed and presented education programs for people with different types of arthritis and for healthcare professionals who wish to enhance their competency in arthritis care.

In 2009, she completed the Advanced Clinician Practitioner in Arthritis Care (ACPAC) program through the University of Toronto and St. Michael's Hospital. She provided ACPAC support in the pediatric rheumatology clinic at Children's Hospital, London, Ontario, and for local physicians and rheumatologists in Guelph and Kitchener-Waterloo from 2009 until 2021. Her passion has been the development of models of care that improve timely and appropriate access to care for people living with arthritis.

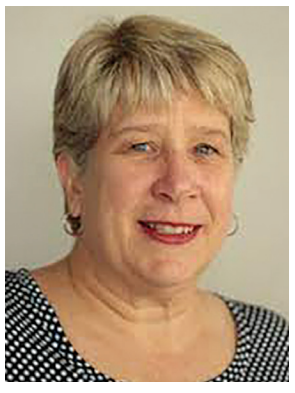
Ms. MacQueen has been a member of the Arthritis Health Professions Association (AHPA) for over 33 years and served as president of the organization from 2018–20 during which time she was focused on the development of a strategic plan and promoting collaboration with the Canadian Rheumatology Association, the Ontario Rheumatology Association and the ARP. She was awarded the AHPA Extraordinary Service Award in 2021 and the AHPA Lifetime Achievement Award in 2022.

In 2022, Ms. MacQueen was awarded the Leadership and Advocacy Award by the Ontario Physiotherapy Association and recently received a Kitchener-Waterloo Oktoberfest Woman of the Year Award for her professional activities.

A proud member of the ARP, Ms. MacQueen has participated in annual meetings and Pediatric Rheumatology Symposiums (PRSYMs) since the 1990s.

"It is a great honor to receive the Ann Kunkel award for advocacy. So many of my colleagues work tirelessly, not only to advocate for their patients, but also within our professions, to create system changes that will improve access to care for people living with arthritis. It is humbling to have been nominated for this award by my peers—people I admire and strive to emulate," says Ms. MacQueen.

Ms. MacQueen recently retired from the Arthritis Rehabilitation and Education Program of the Arthritis Society and is enjoying her new role as proud grandma to three wonderful granddaughters.



Distinguished Scholar Award

The 2022 Distinguished Scholar Award was presented to **Aileen Davis, BScPT, MSc, PhD**, for her exceptional achievements in scholarly activities pertinent to arthritis and rheumatic diseases. Dr. Davis is professor emeritus, University of Toronto, Ontario.

Dr. Davis's primary research focus is musculoskeletal disease, particularly in identifying modifiable predictors of patient outcomes. She has extensive experience in outcome measure development and evaluation and has published and lectured extensively on various aspects of patient evaluation and outcomes in arthritis. Her research has focused on models of care for osteoarthritis (OA), including the development, implementation and evaluation of care pathways to improve access to services for people having total hip or knee replacement, and implementation and evaluation of evidence-based, non-surgical management for people with hip and knee OA.

"I'm extremely honored to be recognized by my peers in the ARP and selected for this award. I've been a member and volunteer with the ARP for many years and this involvement has afforded me the opportunity to meet and collaborate with so many talented members. The ARP community plays a critical role in advocating for and conducting research to improve care and outcomes for people with arthritis," says Dr. Davis.

"It is a privilege to have the opportunities afforded by involvement with the ARP and to receive this award in acknowledgment of my contributions to this role of the ARP. These clinical and research accomplishments would not have been possible without the mentorship and collaboration of my many colleagues, collaborators, trainees and staff, and this award is a testament to their support," she adds.

Dr. Davis trained as a physiotherapist and clinical epidemiologist, receiving her doctorate from the University of Toronto. She was a senior scientist and division head, Division of Health Care and Outcomes Research, Krembil Research Institute, Toronto, and an investigator with the Arthritis Community Research and Evaluation Unit at University Health Network, Toronto.

She continues her academic appointment at the University of Toronto in the Departments of Physical Therapy and Surgery and holds full membership in the School of Graduate Studies in the Rehabilitation Science Institute, Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, and the Institute of Medical Science.

She is a past member of the Musculoskeletal Health and Arthritis Advisory Board of the Canadian Institutes of Health Research, Ottawa. She also is the past chair of the Scientific Advisory Committee, a member of the board of The Arthritis Society, co-chair of Bone and Joint Canada and director of their Osteoarthritis Initiatives and a member of the board of the Osteoarthritis Research Society International. She also was an associate editor for *Osteoarthritis and Cartilage* for six years.

A longstanding member of the ARP, Dr. Davis served two terms as the ARP representative on the Quality Measures Subcommittee, three terms on the Editorial Board of *Arthritis Care & Research* and is currently a member of the Committee on Journal Publications.

Distinguished Clinician Award

The ARP Distinguished Clinician Award is presented to an ARP member who is engaged in clinical practice and demonstrates outstanding clinical expertise in arthritis and the rheumatic diseases. This year two people are receiving the award: **Adena Batterman, LCSW, MSW**, and **Heather Benham, DNP, APRN, CPNP-PC**.

Adena Batterman, LCSW, MSW, is a licensed clinical social worker and senior manager of the Inflammatory Arthritis Support and Education Programs in the Department of Social Work Programs at the Hospital for Special Surgery, New York City. She earned a Master of Social Work from Silberman School of Social Work, Hunter College, New York City.

"I am honored and humbled to receive the ARP Distinguished Clinician Award. Being recognized by my peers and colleagues is a high honor," says Ms. Batterman.

"My volunteer work on ARP Committees, projects and participation in Annual Meetings over the past 20 years has provided many opportunities to learn from passionate, engaged rheumatology professionals from many disciplines. These experiences have expanded my thinking and perspective, helped me discover new directions in my work and have made me a better clinician and researcher. I deeply appreciate and value these relationships and the mentorship I've experienced through the ARP and the ACR," she adds.

Throughout her 27-year career in healthcare, Ms. Batterman's clinical, program and research work has focused on supporting and enhancing patients' ability to cope with the physical and emotional impact of chronic illness. Since 1999, Ms. Batterman has developed and continues to provide strategic oversight to innovative patient-focused support and education programs for people with inflammatory arthritis. These vital forums provide camaraderie for, and a community where people with inflammatory arthritis and their loved ones can learn about inflammatory arthritis management while processing its emotional impact. Ms. Batterman's work focuses on integrating patient perspective into program development and research via focus groups, needs assessments and patient partner input.

To address health disparities in Hispanic rheumatoid arthritis (RA) patients, Ms. Batterman is currently overseeing the development of a culturally tailored, bilingual (i.e., Spanish/English) support and education pilot. This program's approach will incorporate input from Latinx patients with RA, building on evidence-based, culturally tailored outreach and self-management strategies.

Ms. Batterman has served as co-investigator on multiple research initiatives that emphasize patient perspective, including the development of a self-management mobile app for people with lupus and identifying the relevance of Patient Reported Outcomes Measurement Information System (PROMIS) items in systemic lupus erythematosus, as well as principal investigator on studies concerning the self-management needs of people with gout, and the development of a program evaluation tool for an early RA support and education program.

She is currently serving as co-investigator on two qualitative studies: exploring the psychological experience of work for people living with inflammatory arthritis, and the support and education needs of Latinx/Hispanic patients with RA.

Ms. Batterman has also supported the professional growth of social work students and colleagues through individual and peer group supervision and presentations on an integrative biopsychosocial approach to working with patients who have inflammatory arthritis. She has also presented professional educational content for ACR/ARP annual meetings over the past 20 years, including the 2018 Daltroy Memorial Lecture: Healer, Know Thy Patient (and Thyself): What Matters in Patient-Provider Relationships? Values, Attitudes and Beliefs. Most recently, Ms. Batterman authored a new module in the *Fundamentals of Rheumatology Course (FRC)*, titled "Addressing Psychosocial Issues in Rheumatic Illness."

Ms. Batterman has served the ARP in multiple roles and committees over the past 10 years, including as member of the Practice Committee, Executive Committee, liaison to the Committee on Education and, most recently, as chair-elect of the eLearning Subcommittee.

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Heather Benham, DNP, APRN, CPNP-PC, has been a certified pediatric nurse practitioner in the Rheumatology Department at Scottish Rite for Children, Dallas, for nearly 20 years. She received her Doctor of Nursing Practice and Master of Science in Nursing from the Frances Payne Bolton School of Nursing at Case Western Reserve University, Cleveland.

She is a member of the Childhood Arthritis and Rheumatology Research Alliance (CARRA), where she is the research coordinator for the CARRA registry and is active in the Musculoskeletal Ultrasound Workgroup. She holds certification in musculoskeletal ultrasound through the ACR.

Dr. Benham loves to interact with her patients and families through the use of bedside ultrasound, both for diagnostic and interventional purposes. She has also developed a musculoskeletal ultrasound curriculum for the pediatric rheumatology fellows at her institution.

"I am very honored to be receiving the ARP Distinguished Clinician Award. I have been working as a nurse practitioner in pediatric rheumatology for nearly 20 years and it is wonderful to be honored for the clinical work for which I am so passionate," says Dr. Benham. "I owe much of my success to the team I work with on a daily basis and the patients and families who continue to amaze me with their resilience."

As a member of the ARP, Dr. Benham has served as the ARP representative to the Committee on Rheumatologic Care, as well as serving on the ARP Practice Committee, the ACR/ARP Annual Meeting Planning Committee and the Nurse Practitioner/Physician's Assistant Curriculum Task Force. She currently is the ARP representative to the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the ARP representative to the Rheumatology Research Foundation Impact Advisory Council.

Dr. Benham's conference presentations include A Swollen Joint: The Nuts and Bolts of Pediatric Rheumatology, 2014 Regional CME Conference, Texas Academy of Physician Assistants; Update on the Treatment of Juvenile Idiopathic Arthritis, 2015 Conference on Pediatric Health Care, National Association of Pediatric Nurse Practitioners; The Use of Ultrasound Guided Steroid Injections in the Treatment of Juvenile Idiopathic Arthritis (JIA), Pre-Brandon Carrell Conference, Texas Scottish Rite Hospital, June 2016; and A Swollen Joint: An Overview of Juvenile Idiopathic Arthritis (JIA) and Related Conditions, Pediatric Orthopaedic Practitioners Society Annual Conference, May 2018. She has numerous publications to her name and has served as the Scottish Rite study coordinator for research trials.

Distinguished Educator Award

This year's Distinguished Educator Award was presented to **Linda Li, PT, PhD,** for demonstrating excellence in teaching patients and students/trainees. Dr. Li is a professor and Harold Robinson/Arthritis Society Chair in the Department of Physical Therapy, University of British Columbia, Vancouver, and senior scientist at Arthritis Research Canada, Vancouver.

"I am extremely honored to be selected for this award. My work focuses on patient-oriented research and there is nothing more gratifying than seeing our students collaborate and co-produce research with patients. This award is shared with all the patient partners who have so generously given their time, expertise and lived experiences for educating a generation of researchers in patient-oriented rheumatology research," says Dr. Li.

"As a pioneer in engaging patients as research partners, Arthritis Research Canada provides an unparalleled environment for me to grow as a researcher and an educator. I am also grateful for the important support of the University of British Columbia," she adds.

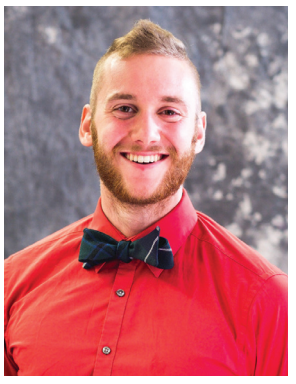
Dr. Li's research in knowledge translation and implementation science centers on strategies to improve the care of people with arthritis and to support patient self-care. Her work focuses on the integration of online, mobile and wearable tools to improve clinical practice. An example includes physical activity counseling by physical therapists with the use of wearables and apps. The latter includes OPERAS (On-demand Program to EmpoweR Active Self-management), an award-winning self-monitoring app co-designed with and for people with rheumatoid arthritis.

Dr. Li's work in integrated knowledge translation has led to a new line of studies on the benefits of engaging patients in the research process. Since 2014, she has mentored trainees to study the experiences of patients as research partners and examined the benefits and risks of being research partners from a patient perspective. The results highlight important elements of a mutually beneficial partnership between patients and researchers, and subsequently inform two new products: 1) a conceptual framework of meaningful patient engagement in research, and 2) an outcome measure for evaluating the quality of patient engagement. Many of Dr. Li's mentees have built successful careers in knowledge translation and implementation research (in academia) and practice (in health authorities and research centers).

Dr. Li's work has been recognized with several awards, including the Michael Smith Health Research BC (British Columbia) Career Investigator Award and a Canada Research Chair in Patient-Oriented Knowledge Translation. She was selected for the ARP Distinguished Scholar Award in 2015. In 2019, she was inducted as Fellow of the Canadian Academy of Health Sciences.

Outstanding Student in Rheumatology Award

The ARP Outstanding Student in Rheumatology Award seeks to recognize students advancing rheumatology in one or more of the following areas: education, practice, research and/or advocacy, and is open to non-physician health professional students who have not yet achieved the highest academic degree in a given field of study. Two people received the award this year: **Thomas Bye, PT, DPT, MS**, a licensed physical therapist and PhD student at the University of Delaware, Newark, and **Hannah Peterson, PharmD**, a pharmacy practice resident at Methodist University Hospital, Memphis, Tenn.



Thomas Bye, PT, DPT, MS, received a Bachelor of Science in exercise science in 2018 and a Master of Science in kinesiology in 2019, both from Michigan Technological University, Houghton, and a doctorate in physical therapy from the University of Delaware in 2021, where he is beginning work as part of a dual doctor of physical therapy and doctorate in biomechanics and movement science degree program.

His interests span from clinical practice in orthopedics and older adults to human performance and space physiology. His current research with osteoarthritis, physical activity, sedentary behavior and functional outcomes is part of the Delaware ACTIVE lab, directed by his mentor, Daniel K. White, ScD. Last year, Dr. Bye and his colleagues at the university presented research that demonstrated the Hawthorne effect when monitoring physical activity of adults with knee osteoarthritis.

Dr. Bye is a member of the ARP Practice Committee and integrative treatment clinical practice guidelines review team, which aims to improve non-pharmacological treatment of rheumatoid arthritis and improve interdisciplinary practice for patients with rheumatic diseases. Additionally, he is currently a mentee in the Rheum with a (re)View initiative preparing to conduct journal reviews.

"I am grateful for the opportunities and work that I have taken part in at the ARP, and the Outstanding Student award is humbling. I am very excited to continue researching and supporting my peers and patients," says Dr. Bye.

Hannah Peterson, PharmD, received her Doctor of Pharmacy from Lipscomb University College of Pharmacy, Nashville, in 2022, and is currently in her pharmacy practice residency at Methodist University Hospital. While at Lipscomb, Dr. Peterson was selected as a participant in the prestigious Vanderbilt Program of Interprofessional Learning, which brings together pharmacy, medical, nursing and counseling/social work students. She also served as a pharmacy intern at Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville.

While exploring areas of interest during pharmacy school, Dr. Peterson was intrigued by the love and passion Kam Nola, PharmD, MS, FAPhA, professor and chair of the Department of Pharmacy Practice at Lipscomb University College of Pharmacy and Health Sciences, has for rheumatology. She sought out research opportunities in this field and was introduced to Anna Patrick, MD, PhD, assistant professor of pediatrics and rheumatology, Vanderbilt University.

"Receiving the Outstanding Student in Rheumatology award means a lot to me as it is a great accomplishment in my early professional career and reflects my passion and dedication to my research in juvenile idiopathic arthritis," says Dr. Peterson.

"I was first introduced to involvement in rheumatology with Dr. Kam Nola, who deservingly won last year's ARP Distinguished Educator Award. I was then introduced to Dr. Anna Patrick, with whom I have been conducting research in juvenile idiopathic arthritis (JIA) for the last two years. Through this project we hoped to develop electronic health record algorithms that continue to facilitate research in JIA. It is highly rewarding to see our work further recognized and appreciated through this award," she adds.

"Although I currently am undecided about plans for after residency and specialization, I hope that involvement in rheumatology, whether through practice, research or volunteering, is in my future," Dr. Peterson says. **R**

Patrice Fusillo is a writer and editor based in Oakland, Calif.

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ACR Distinguished Fellows

Honoring 10 clinical & research rheumatology fellows

■ BY PATRICE FUSILLO

Each year, the ACR honors up to 10 clinical and research fellows who have performed meritoriously. Meet this year's Distinguished Fellows, who are bridging the gap between research and patient care, and who were recognized at ACR Convergence 2022 in early November in Philadelphia. ***Editor's note:*** Visit our website to learn more about these Distinguished Fellows: **https://tinyurl.com/3v3p35ns**.

Fatima Alduraibi, MD, PhD

Instructor, Division of Immunology and Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston

"I am honored and thrilled to have been named as one of the ACR Distinguished Fellows. It is a reflection of the outstanding support by exceptional mentors who allowed me to grow as a physician scientist and enabled me to enrich my area of interest in lupus nephritis and become a growing expert in the field," says Dr. Alduraibi.

Rebecca B. Blank, MD, PhD

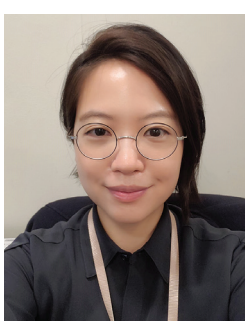
Post-Doctoral Research Fellow/Instructor, Division of Rheumatology, New York University (NYU) Grossman School of Medicine, New York City

"I am so honored and grateful to receive a Distinguished Fellow Award from the ACR this year. I deeply appreciate all the support from my mentors and patients I have had in my career and especially during my fellowship training at NYU without which I would not have been able to achieve this honor. It is humbling to follow in the footsteps of former ACR Distinguished Fellows, many of whom are current colleagues and mentors!" says Dr. Blank.

Michael Loncharich, MD

Acting Associate Program Director, Rheumatology Fellowship, Walter Reed National Military Medical Center, Bethesda, Md.; and Assistant Professor, Uniformed Services University of the Health Sciences, Bethesda, Md.

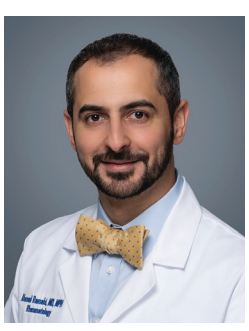
"I'm honored to receive the ACR's Distinguished Fellow award. The award validates that my clinical, research and education endeavors are not only interesting to me, but also are seen as beneficial to the broader rheumatology community and our patients. I've been lucky to have had amazing mentors at Walter Reed and the National Institutes of Health along the way and hope to help future rheumatology fellows master their clinical skills and pursue their career goals," says Dr. Loncharich.



Elizabeth Park, MD, MSc

Assistant Professor, Division of Rheumatology, Columbia University Irving Medical Center, New York City

"It is a tremendous honor to be recognized for my work as a research and clinical fellow, and I am deeply grateful for our patients and the mentorship I have received thus far," says Dr. Park.



Ahmad Ramahi, MD, MPH

Research Fellow, Scleroderma Program, Division of Rheumatology, University of Michigan, Ann Arbor

"I am beyond honored to receive the ACR Distinguished Fellow award. This award magnifies the importance of research in rheumatology and fuels my motivation and passion for working in the scleroderma field and serving my community. I am thankful to my mentors in the scleroderma program and the University of Michigan rheumatology division who invested in me, and, without their support, I wouldn't have achieved this," says Dr. Ramahi.

Didem Saygin, MD

Assistant Professor of Medicine, Division of Rheumatology and Clinical Immunology, University of Pittsburgh

"Being selected as one of the ACR Distinguished Fellows is an honor and testament to my mentors and everyone who supported me along the way. I am also very grateful to the ACR for supporting trainees—at every stage—and rheumatologists across the U.S.," says Dr. Saygin.

Melanie H. Smith, MD, PhD

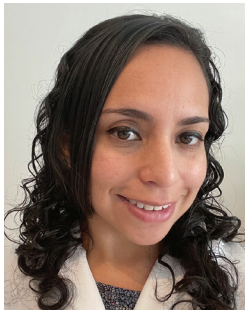
Assistant Attending Physician, Division of Rheumatology, Hospital for Special Surgery, New York City; and Assistant Professor of Medicine, Weill Cornell Medical College, New York City

"It is an incredible honor to receive the ACR Distinguished Fellow award. It is a testament to the opportunities I have had during my fellowship training and the amazing group of mentors that have supported my development as both a physician and a scientist. I am excited to embark on a career dedicated to understanding mechanisms of disease, with the goal of improving care for our patients," says Dr. Smith.

Ajay Tambralli, MD

Assistant Professor, Divisions of Rheumatology and Pediatric Rheumatology, University of Michigan, Ann Arbor

"I am very grateful to be named an ACR Distinguished Fellow. This award attests to the support of the many mentors and colleagues I have worked with over the years, who have molded me into the person I am today. I am thankful to the ACR for this recognition and will continue striving to become a better physician-scientist and a valuable citizen in the rheumatology community," says Dr. Tambralli.



D. Sofia Villacis Nunez, MD

Assistant Professor of Pediatrics, Division of Pediatric Rheumatology, Emory University School of Medicine/ Children's Healthcare of Atlanta

"I am deeply honored and humbled to receive the ACR Distinguished Fellow award as a recognition of all the efforts that have gone into my education and research during fellowship. I am truly grateful to my mentors, who have guided me in my path and have made this award possible, and I am excited to continue to share with them a career in academia, to keep spreading the knowledge in pediatric rheumatology and supporting the efforts to improve the health of children with rheumatic diseases," says Dr. Villacis Nunez.

Rachel Wallwork, MD

Clinical Fellow, Division of Rheumatology, Johns Hopkins University, Baltimore

"I am honored to be selected as an ACR Distinguished Fellow. I have been extremely fortunate to learn from an incredible and inspiring group of mentors and co-fellows. I look forward to continuing to study lung involvement in systemic sclerosis to gain a deeper understanding of how harnessing baseline clinical, radiographic and serologic biomarkers can enable prediction of pulmonary function decline and major adverse events. Eventually, I plan to explore methods for predicting which patients will respond to specific treatments. I believe that this type of precision medicine is essential for improving outcomes for patients with systemic sclerosis and other rheumatic diseases," says Dr. Wallwork. **R**

Patrice Fusillo is a writer and editor based in Oakland, Calif.

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plex medical issues with expectations of scholarly activity intended to benefit their patients and community.

Senior author Christina Downey, MD, a rheumatologist at Loma Linda University School of Medicine, also notes that the evaluation and management codes tend to undervalue the revenue generated by a rheumatologist. *Example:* She says that after adjusting for inflation, Medicare reimbursement for the evaluation and management code 99214, which is used for care requiring moderate complexity medical decision making or a total of 30–39 minutes devoted to the encounter on the date of the visit, has remained stagnant from 2005 to 2020. This finding is true despite the increase of indirect overhead costs, such as hospital administrative, financial and legal operations.

The authors hope their study will help individuals in positions of leadership in academic health systems use the overall value rheumatologists bring to the health system as an argument for higher compensation or more protected time for clinical academic rheumatologists.

"What we are trying to do with this paper is to arm practicing rheumatologists with the knowledge of the value that they bring," says Dr. Downey, noting that rheumatologists are cognitive specialists who, unlike orthopedic surgeons, cannot rely on high volume procedures.

In their article, the authors note that interventional cardiologists are well compensated due, in part, to the revenue brought to the hospital system by their procedures, and they argue the same consideration should be given to rheumatologists. **R**

Lara C. Pullen, PhD, is a medical writer based in the Chicago area.

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ACR Proposes New ICD-10 Code to Capture 'Pre-RA'

FROM THE COLLEGE

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On Sept. 13, the ACR and Kevin D. Deane, MD, PhD, rheumatologist at the University of Colorado, Aurora, presented a proposal to create a new clinical code to recognize "pre-rheumatoid arthritis" to the International Classification of Diseases Coordination and Maintenance Committee (ICD-10 C&M) at the Centers for Medicare & Medicaid Services (CMS).

The International Classification of Diseases 10th Revision, or ICD-10-CM, is the Health Insurance Portability and Accountability Act (HIPAA) code set standard for reporting diagnoses in all healthcare settings. ICD-10-CM is a U.S. clinical modification of the World Health Organization's ICD-10. These codes help ensure the accuracy, protection and accessibility of health information.

Twice each year, organizations have the opportunity to present diagnosis code proposals to the ICD-10 C&M for consideration. This federal committee, which includes the CMS and the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS), focuses on the clinical issues for a condition, procedure or technology and is responsible for approving ICD code changes, diagnosis errata, addenda and modifications.

The ACR's code change request proposes a new code and definition for pre-rheumatoid arthritis (pre-RA), a condition in which an individual may exhibit RA-related autoantibodies without the clinical condition (i.e., inflammatory arthritis) of RA. The proposed new code and definition is: R76.81: "Abnormal rheumatoid arthritis-related immunologic findings without current or prior diagnosis of clinically apparent inflammatory arthritis."

Rationale

The code proposal included a rationale for why a pre-RA code is needed.

RA is a well-known autoimmune condition characterized by the presence of inflammatory arthritis. Up to 80% of individuals with RA may also have abnormalities in circulating biomarkers, including but not limited to the autoantibody rheumatoid factor (RF) and antibodies to cyclic citrullinated proteins (CCP).

The current paradigm for the diagnosis and treatment of RA is for a clinician to identify joint findings that are determined to be clinically apparent IA, diagnose the condition as RA and initiate treatment. This is the typical clinical situation in which the existing ICD-10 codes for RA (e.g., M60.XXX, M50.XXX) are applied.

However, it is now well established that RA-related immunologic tests, such as RF and CCP, can be positive in individuals in the absence of and prior to the appearance of inflammatory arthritis and are predictive of future onset of clinical RA—a period that can be termed "pre-RA." Further, individuals who have abnormal RA-related immunologic tests without inflammatory arthritis are being identified in growing numbers in clinical care.

Medically appropriate counseling approaches are currently available and can help individuals in this pre-RA state gain awareness of RA, its symptoms, the importance of medical follow-up to watch for the development of treatable inflammatory arthritis, and lifestyle changes (e.g., smoking cessation) that may lower their risk for developing RA. In addition, the predictive ability of RF and anti-CCP for future clinical RA has underpinned multiple clinical observational studies and prevention trials in RA, and it is expected that there soon will be approved pharmacologic therapies for RA prevention.

Importantly, although existing ICD-10 codes can be used to designate clinical RA, as well as RF and anti-CCP positivity, there is not currently a clear way in the existing ICD-10 system to designate individuals who may exhibit RA-related biomarkers but do not have clinically apparent inflammatory arthritis. As such, the introduction of a new code to accurately designate an individual who has abnormal RA-related immunologic tests will facilitate clinical designation and care of these individuals, as well as facilitate clinical research.

Next Steps

The ACR presented the case for this new code to the CDC and received some initial feedback that included shortening the term, as well as including the specific laboratory tests that would qualify this code. A suggested revision is: "Anti-cyclic citrullinated peptide antibody (anti-CCP) and/or rheumatoid factor (RF) positivity without a current or prior diagnosis of rheumatoid arthritis."

Final decisions on code revisions are made through a clearance process within the U.S. Department of Health & Human Services. The ACR expects to receive formal feedback around mid-November, after which we will address any comments and plan to move forward with finalizing this new code.

Questions on ICD-10 or the code change proposal can be sent to Antanya Chung at **achung@rheumatology.org** or **practice@rheumatology.org**. **R**

continued on page 47

To Prescribe Is Humane (Unless You're in Texas)

A fable for our times

■ BY RAYMOND SCALETTAR, MD, DSc

This invasion of the patient's privacy & coercion of the physician is justified in Texas because the state has determined it owns, & therefore can make decisions pertaining to, a woman's body.

You are a rheumatologist in Texas. You are very well trained. Your mentors included some of the leaders in rheumatology, and you are respected by your colleagues and your patients. You know the devastation of untreated rheumatoid arthritis and lupus.

A young woman with recent onset of systemic lupus erythematosus is your new patient. You discuss the indications and side effects with her, and you both agree that, in her case, methotrexate is the drug of choice. You are well aware of the ACR's guidelines relating to the use of this drug when there are issues of reproductive health.[1] The risks of pregnancy with methotrexate are discussed as part of the informed consent process. The patient concurs and takes oral contraceptives for several months before initiating treatment with methotrexate.

After starting treatment, and despite using oral contraceptives, your patient becomes pregnant. (*Author's note:* Oral contraceptives have a pregnancy prevention failure rate upward of 5%.[2]) The patient did not realize she was pregnant because her menstrual cycles have been irregular since she became ill. However, she begins to have pain and severe bleeding, evidence of a spontaneous miscarriage.

A formerly friendly neighbor who is short of cash and is now a bounty hunter becomes aware of her plight and reports her to the authorities.[3] The accusation is that she has induced an abortion.

The new pharmacist who refused to renew your methotrexate order for the patient justified that action based on suspicion that you are using it as a abortifacient because you did not indicate on the renewal prescription that it is being used to treat the patient's lupus.[4-6] You note the drug is used for multiple ailments, and it is not the role of a pharmacist to determine the suitability of a medication for a patient.[7,8]

Your happy days as a rheumatologist are over. The joyful days of being a dedicated physician who believed in the sanctity of the doctor–patient relationship is now a myth. The patient's constitutionally protected rights and the right to privacy that existed prior to the U.S. Supreme Court decision in *Dobbs v. Jackson Women's Health Organization* are over in the state of Texas.

The Aftermath

You are accused of inducing an abortion and await your deposition. You ponder the questions: Did you induce the abortion deliberately? *Of course not.* Then why did you prescribe methotrexate knowing it can induce abortion? Did you conspire with the patient to end the pregnancy because you both feared the toxic effects on the fetus?

In its June 24 decision in *Dobbs*, the Supreme Court (SCOTUS) quoted a Mississippi law that states abortion is "demeaning to the medical profession."[9] But you wonder whether instead it is SCOTUS that is now demeaned. And with all your vaunted training and accolades, you have been thrust into the time warp of Texas' inner sanctum horrors and its post-*Dobbs* antediluvian laws in which social media—but not a doctor—can be consulted for pregnancy care.

It was you who sent the patient to the emergency department because she was bleeding heavily. The obstetrician on call knew the rules of EMTALA [the Emergency Medical Treatment and Labor Act], requiring that one must treat an emergency, and determined the patient required an emergency abortion.[10-12] Your colleague has an outstanding reputation for providing pregnant patients with evidence-based, essential healthcare.

Although this patient needed, and met, medical criteria for emergency care, she did not meet *political* criteria allowing for an exception to prohibited abortions. That exception, found in Section 170A.002 of Texas' law, mandates that an abortion could be performed to save a mother's life when "the pregnant female ... has a life-threatening physical condition ... arising from a pregnancy that places the female at risk of death ... ."[13] Because the patient was not in shock, only had a rapid heartbeat and her hematocrit was only down to 30%, she was not yet at "death's door."

The obstetrician also knew of the September 2021 *amicus* brief, submitted in *Dobbs* by the American College of Obstetricians and Gynecologist, the American Medical Association and many other medical organizations, that stated "abortion is a safe and essential component of healthcare."[14]

The obstetrician questions why risk of a patient's death is to be ignored just because bureaucrats sitting safely in their offices have issued laws that go against sound medical science. They have no understanding of emergent obstetrical issues or reproductive health and have provided no directives on what a physician is to do when faced with a medical situation that requires immediate attention.

The state has created a classic catch-22 conundrum for physicians. It has barred physicians from relying on their professional judgment and traditional medical standards and procedures, and coerced compliance with the Texas law by threatening fines and imprisonment for its violation. But the state has not issued any alternative standards and procedures to be used in lieu of the best practices of medical treatment. This places you and the obstetrician in triple jeopardy: You may be sued for malpractice for failure to treat, lose your license, and be fined and go to jail.

You both are indicted and await trial. Are you now part of the new world of the criminalization of medical care?[15] You reflect on how you have spent your entire career in medicine treating all those in need, regardless of their economic circumstances. This has been your calling. Your obstetrical colleague has been known to prescribe misoprostol and mifepristone for first trimester abortions, consistent with sound medical practice. But the state has taken steps to restrict access to these life-saving medications.

The pharmacist who refused to fill your order for methotrexate for your patient aided the state in its effort to restrict access to medication by demanding written details about the patient beyond that routinely and legally required to fill a prescription. Aside from violating a federal law (i.e., the Health Insurance Portability and Accountability Act of 1996 [HIPAA]), which protects a patient's privacy, collection of protected medical information created a paper trail the state and others could follow, leading from you and your patient to the pharmacy, then to the healthcare insurer and even to the patient's employer.[16] This invasion of the patient's privacy and coercion of the physician is justified in Texas because the state has determined it owns, and therefore can make decisions pertaining to, a woman's body.

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On July 14, the Office for Civil Rights in the U.S. Dept. of Health & Human Services issued guidance that unequivocally stated that discrimination against a pregnant person, including denial of medication, is neither justified nor allowed under federal law: "Pharmacies ... may not discriminate ... with regard to supplying medications; making determinations regarding the suitability of a prescribed medication for a patient. ... As recipients of federal financial assistance, ... pharmacies are prohibited from discriminating on the basis of race, color, national origin, sex, age, and disability ... under a range of federal civil rights laws. Under federal civil rights law, pregnancy discrimination includes discrimination based on current pregnancy, past pregnancy, potential or intended pregnancy, and medical conditions related to pregnancy or childbirth."[17]

Personhood

You realize you now live in a new world in which a patient with diabetes, autoimmune disease, cancer, mobility problems or neuropsychiatric issues is of no concern to a state ranking 48 out of 51 on healthcare access and quality, service use and cost, health disparities, and health outcomes.[18] And your obstetrical colleague reflects how this state has little interest in the pregnant woman's suffering: potential pain, ectopic pregnancy, fetal chromosomal abnormalities, placenta previa and increased necessity for Caesarean deliveries. The state, which ranks as the fifth worst in the nation for children, is concerned about the concept of fetal personhood, overruling concern for the rights and needs of mothers and children.[19,20]

You have heard the argument that a fetus is a person entitled to all protections accorded any living being. But is it?

Arguments and counter-arguments come from politicians, the courts, religious leaders, medical specialists and other groups with vested interests in the answer and actions that follow. The heart of the conflict is the tension between maternal and fetal rights and what takes priority: protecting the health and, possibly, the life of a pregnant woman or the desire to save a fetus. Who is to make the decision—the woman or some external party claiming authority to do so?

And what is a fetus, especially one that may not be viable? The argument is that it is a "baby" who should be given a chance to live, even at the literal expense of the mother's life. But before the fetus is born is it—can it be—a living human being? If it first has to be born to live, then is a fetus a baby or only a possible baby?

You feel like you are back in your debate class in college, trying to convince your audience of the correctness of your position on the topic *du jour:* syllogisms.

Pushing the academic and intellectual questions aside, you recall the battle being fought today had its genesis in a 1987 court-ordered Caesarean section on a woman dying of cancer who was 26 weeks pregnant. The baby died two hours after the operation, and the mother died two days later. The family sued and, in a 7–1, precedent-setting decision, the D.C. Court of Appeals ruled that a woman has the right to decide about medical treatment for herself and her fetus. It said that only in "rare and exceptional" cases would it be possible to override the mother's wishes and acknowledged that "some may doubt that there could ever be a situation extraordinary or compelling enough to justify a massive intrusion into a person's body, such as a Caesarean section, against that person's will."[21]

What Next?

While you prepare for deposition, you are despondent. You are accused of prescribing methotrexate to induce an abortion and know that Texas law makes performing an abortion a felony, punishable by up to life in prison. You also know that you are facing a huge fine because the law mandates the attorney general seek a civil penalty of not less than $100,000, plus attorney's fees.

The prosecution, citing the National Academy of Medicine's controversial and flawed report To Err Is Human, proclaims that you are part of the problem with the medical establishment and that your treatment of the patient is a criminal offense in Texas.[22]

As you await the court's judgment and contemplate your future, you ask yourself why anyone would want to go to medical school or apply for residency in a state like this. Residency review committees have already documented deficiencies in training in states with injunctions on providing training on such fundamental procedures as dilation and curettage.

Why would any practitioner want to remain in a state with antediluvian laws that compel the practice of bad medicine at the patient's expense over supporting best practices of the medical profession? If you want to practice good medicine, why not head to enlightened states and leave ones like Texas to become medical wastelands?

Finally, you ask when will your colleagues come together across the medical spectrum and exclaim, "We're as mad as hell, and we aren't going to take it anymore!" and then take action?[23]

Wake Up!

Suddenly, you open your eyes. You're in bed and in a cold sweat. You shudder, glance furtively around and whisper, "That sure was a scary nightmare!" Or was it?[24] **R**

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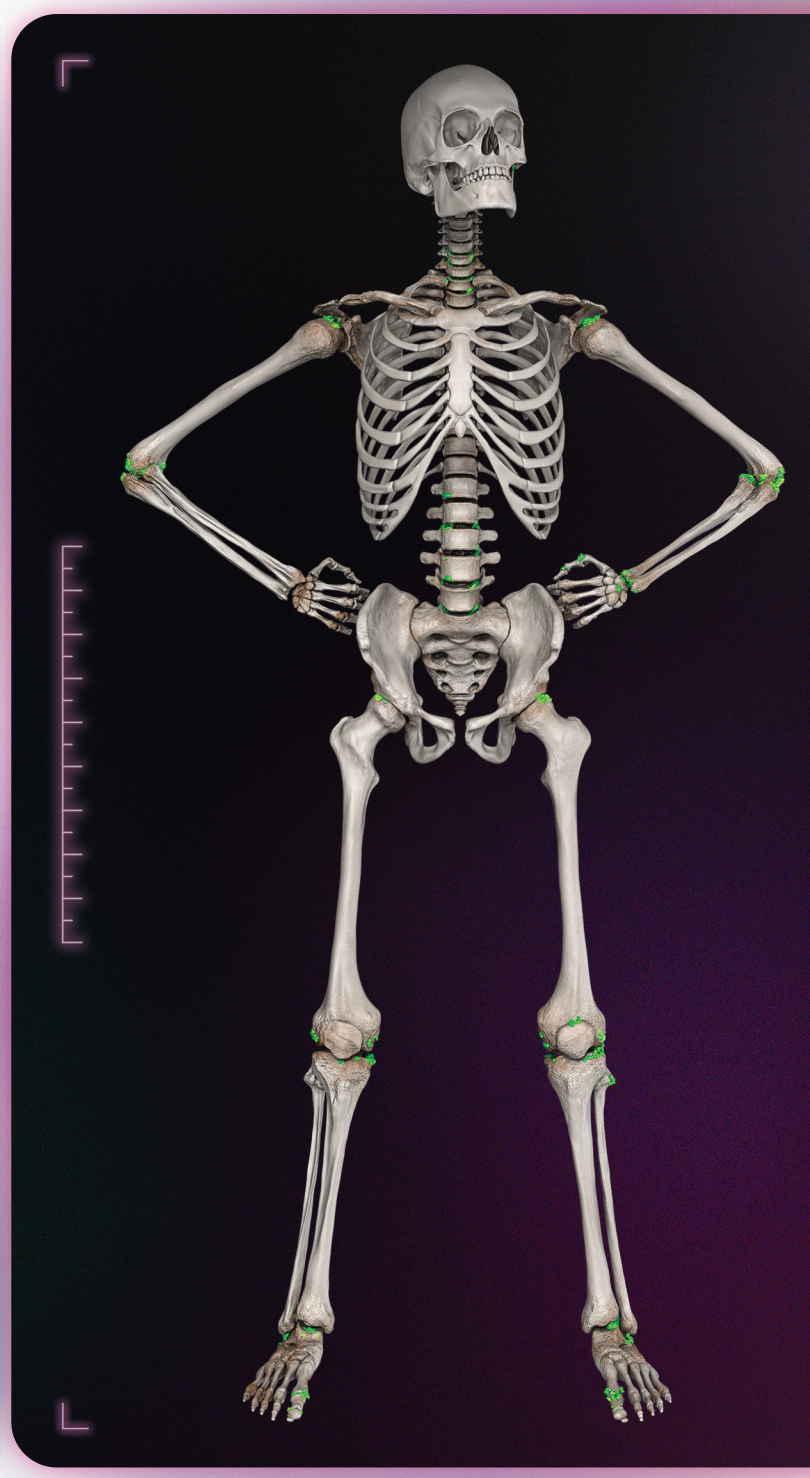


Skeletons are artist rendition.
Hand DECT images and MSU volume are from an actual patient. Individual results may vary.

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

MORE THAN

↑80%

RELATIVE IMPROVEMENT
in efficacy[1]

↓87%

RELATIVE REDUCTION
in infusion reactions[1]

MSU: 0.08 cm^3
(After 13 infusions)

NOW FDA APPROVED

KRYSTEXXA with methotrexate

IMPROVED EFFICACY
REDUCED INFUSION REACTIONS
IMPROVED CONFIDENCE

- **Improved Efficacy:** >80% relative improvement in patient response; 71% (71/100) vs 39% (20/52) complete response* compared to KRYSTEXXA alone at Month 6[1]
- **Reduced Infusion Reactions:** 87% relative reduction in infusion reactions; 4% (4/96) vs 31% (15/49) compared to KRYSTEXXA alone[1]
- **Improved Confidence:** With fewer infusion reactions and improved patient response you can confidently reduce years of urate burden

Discover more about KRYSTEXXA with methotrexate at ReduceUrateBurden.com

52-week, randomized, double-blind trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg Q2W co-administered with 15 mg oral methotrexate QW and 1 mg oral folic acid QD vs KRYSTEXXA alone.[1,2]

sUA, serum uric acid.

*Complete sUA response: The primary efficacy endpoint was the proportion responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

DECT is a dual-energy computed tomography—it can reveal uric acid deposits (in green) throughout the body, including soft tissue deposits, like tendons and ligaments.

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

Congestive Heart Failure: KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following pages.

REFERENCES: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon.
2. Botson J, et al. *J Clin Rheumatol*. 2022;28:e129-e134.

HORIZON

KRYSTEXXA® pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment.

Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency *[see Contraindications]*. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials.

In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study.

Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis *[see Warnings and Precautions]*
- Infusion Reactions *[see Warnings and Precautions]*
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia *[see Warnings and Precautions]*
- Gout Flares *[see Warnings and Precautions]*
- Congestive Heart Failure *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 24-week clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	KRYSTEXXA 8 mg every 2 weeks (N=85) n[a] (%)	Placebo (N=43) n (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively *[see Data]*.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, a total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

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

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria, nausea or vomiting.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA *[see Warnings and Precautions, Adverse Reactions]*
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

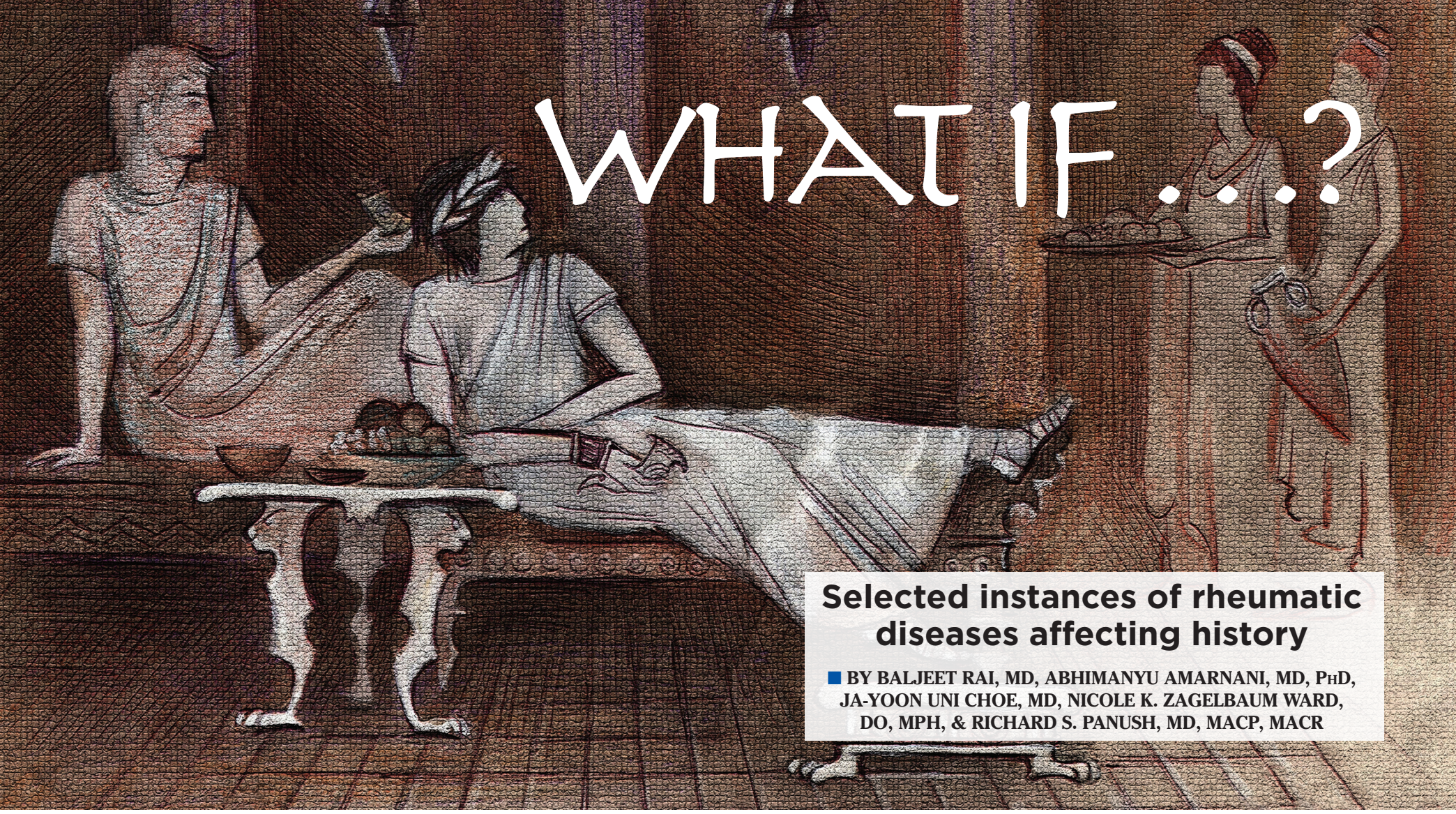
Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known *[see Warnings and Precautions, Contraindications]*.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland

US License Number 2022
Distributed by:
Horizon Therapeutics USA, Inc.
Deerfield, IL 60015



WHAT IF...?

Selected instances of rheumatic diseases affecting history

BY BALJEET RAI, MD, ABHIMANYU AMARNANI, MD, PhD, JA-YOON UNI CHOE, MD, NICOLE K. ZAGELBAUM WARD, DO, MPH, & RICHARD S. PANUSH, MD, MACP, MACR

Medical conditions have profoundly influenced historical events.

The study of rheumatology (and medicine) in art, history, literature and music is engaging and informative.[1-12] In this article, we present some instances when rheumatic and autoimmune diseases in certain individuals may have affected the course of history in Western civilization.

Physicians are usually concerned, appropriately, with the effects of illness on the lives of individuals. However, medical conditions have also profoundly influenced historical events. Here, we explore how rheumatic disease may have affected historical events. Some examples listed in Table 1 (see opposite) are not discussed.

The history of rheumatology is beyond the scope of this article, but some observations are pertinent to our discussion.[13-16] Representations of what we now know as osteoarthritis, gout, infectious arthritis and possibly spondyloarthritis exist in antiquity; it was only relatively recently that rheumatoid arthritis (RA) and the other rheumatic disorders, particularly the systemic rheumatic diseases, such as systemic lupus erythematosus and vasculitis, were recognized and distinguished from other disorders.[5,9,11,14,16] Most experts agree that systemic rheumatic diseases were not generally recognized until about the 18th century.[11]

Examining the history and evolution of our identification and understanding of rheumatic disease is not only of inherent intellectual interest, but adds perspective to current thinking and practice. When and how rheumatic diseases occurred, or were first recognized, provides insights about possible etiology and pathogenesis. RA is such an example. It was first described in about 1800 CE, coinciding with an increase in sugar consumption in Europe and associated with increased periodontal disease linked to the bacteria *P. gingivalis*. *P. gingivalis* infection is recognized as a risk factor for the development of RA in certain individuals due to the bacteria's ability to citrullinate proteins.[5]

Saturnine Gout, Lead Intoxication & the Fall of the Roman Empire

The culture of the Western Roman Empire, for most of its 500 years (from the first century BCE to the fifth CE), had a profound and lasting impact on the arts, science and religion. Its power declined considerably in Western Europe until the Germanic barbarian King Odoacer deposed the last Western Roman emperor in 476 CE. Causes for the fall of Rome remain controversial, and historians have posited poor leadership, weakened military power and climate change as possible reasons. But what if an important factor in the demise of the empire was lead poisoning from daily wine and food intake of the aristocracy?

Gout was prevalent in ancient Rome and was described— and satirized—among the wealthy by notable Romans, such as Virgil and Galen.[7,17-19] Many Roman Emperors between 15 and 225 CE were known to be heavy consumers of wine and food, and were described as having symptoms potentially consistent with chronic lead intoxication, including severe neuropsychiatric disturbance, neuromuscular dysfunction, gout and abdominal pain.

The principal source of lead poisoning likely stemmed from a grape-based

FIGURE 1A AND 1A PT 2

Tsar Nicolas II's—in whose army the grandfather of one of the authors, Dr. Panush, fought during the Russo-Japanese War of 1905—palace and hunting preserve at the Bialowieza Forest, now in eastern Poland, a short wagon ride from the *shtetl* [village] of the Panush family.

YULIA SEROVA / SHUTTERSTOCK.COM

sweetener common in Roman wine. It was produced by boiling grapes in lead-lined vessels, resulting in lead levels in wine ranging from 240–1,000 mg/L. Given that the Romans consumed approximately 1–5 L of wine per person, lead toxicity may have been widespread.[20] Worse yet, city pipes, cookware and utensils were also lined with lead. Thus, it is estimated that aristocrats consumed ≥250 mcg/L of lead daily. Consider this: The U.S. Occupational Safety and Health Administration (OSHA) has set 50 mcg/L as the limit of what's safe to consume.[20]

What if … Roman emperors had not been encephalopathic as a consequence of their lead intoxication and saturnine gout? How different might world history have been?

TABLE 1

WHAT IF … ?
Roman emperors had not been encephalopathic as a consequence of their lead intoxication and saturnine gout? How different might world history have been?[17-21]
King Herod and/or Herod Antipas, his son, both aristocrats, had not been such prolific consumers of Roman wine or had been abstemious? Might the beginnings of early Christianity and the destruction of the Second Temple have been different?[7,8,22,23]
William Pitt, the British prime minister who was influential and sympathetic to the colonies, did not have an acute episode of (saturnine) gout on the eve of that fateful parliamentary debate that led to the passing of the Stamp Act? How different might American and British history have been?[17-19,24]
King Asa's reign was not disrupted by gout? How different might the history of Judea have been?[25]
The gout of Charles V, as well as his syphilis, had not confounded his rule and contributed to the disintegration of the Holy Roman Empire? How different might European history have been?[26]
Dinosaurs (or at least T Rex) were not afflicted with gout? Might they not have become extinct? How different might evolution had been?[27]
Columbus had not suffered reactive arthritis that affected and limited his voyages of discovery? How different would modern history have been?[28-32]
The pharaoh and/or Moses did not have spondyloarthritis (or DISH)? How different might the biblical exodus have been?[33]
Great King Sejong, presiding over a golden era of Korean culture, had not died prematurely with his spondyloarthritis?[34]
Napoleon hadn't (likely) taken excessive pain medication (likely narcotic) for his thrombosed hemorrhoids on the eve of the epic battle at Waterloo, impairing his leadership and presaging his defeat? How different might modern European history have been?[35,36]
Tsarevich Alexei did not have a near-fatal episode of hemophilia (possibly with attendant arthropathy) at the royal hunting lodge, leading the tsarina to involve Rasputin in her confounding governance of the country while Nicolas was at the front ("if there had been no Rasputin, there would have been no Lenin" [Alexander Kerensky])? How different might 20th century history have been?[37-41]
Hitler had giant cell arteritis and could have been treated? How might that era have differed?[42,43]
John F. Kennedy had not been symptomatic from autoimmune adrenal insufficiency and inflammatory spine disease, was not consuming a daunting cocktail of analgetic and other mind-altering medications, and did not need to wear a back brace on that fateful day in Dallas? How different might his presidency and the history of those times have been?[44-50]
George H.W. Bush didn't develop hyperthyroidism (or didn't acquire it from Millie the dog, who had lupus) or had it sufficiently well controlled so as to preclude the presidential debacle with the Japanese prime minister? Might he have been reelected and the history of that time been different?[51-56]

Saturnine Gout, Lead Intoxication, King Herod the Great & Herod Antipas

At least six prominent *Herods* exist in history, literature, opera and the Bible; they are often conflated, making the interpretation of, and speculation about, their possible medical illnesses challenging.[7,8,22]

King Herod I (the Great) lived from 73 BCE to 4 BCE in Judea. He was known for his cruelty; his accomplishments included economic and diplomatic successes before the onset of mysterious symptoms and his death due to unknown causes.

The historian Flavius Josephus recorded the life and death of King Herod I, describing symptoms of paranoia, depression, psychosis, high fall risk and extreme forgetfulness. Josephus wrote of Herod that, days before death, his "entrails were … ex-ulcerated." He described the violence of Herod's pain in his colon, "aqueous and transparent liquor" about his feet and matter at the bottom of his belly. "His privy member was putrefied and produced worms … when he sat upright. He had a difficulty of breathing, … convulsions … choleric … like a mad man."[23] Symptoms of edema in his lower extremity, dyspnea, abdominal distension and pain, scrotal edema and muscular spasms were described. Lead poisoning and saturnine gout were among an extensive possible differential diagnosis.

Herod the Great's son, Herod Antipas (21 BCE–39 CE), was tetrarch of Judea and Perea, and the subject of artistic depictions, among which is *Salome*, the opera by Richard Strauss (*Author's note:* derived from an Oscar Wilde play that was inspired by a Gustave Moreau painting), in which the tetrarch ordered the murder of every male under age 2, killed his own sons and executed John the Baptist at the whim of his teenage daughter.[7,8]

This Herod clearly experienced dementia, hallucinations, paranoia, heavy use of alcohol and drinking the emperor's wine—a habit perhaps influenced or encouraged by his father's behaviors—violence, twitches and sterility. Different interpretations also show him with falls, chills, shaking, thirst, forgetfulness and sleepiness.
We favor the diagnosis of chronic lead intoxication. He had compatible symptoms (e.g., encephalopathy and neuromuscular abnormalities) and consumed excessive quantities of imperial wine, known to be highly contaminated with lead and likely associated with similar symptoms among Roman aristocracy.[7,8]

What if … King Herod the Great and/or Herod Antipas had not been such prolific consumers of Roman wine? Might the beginnings of early Christianity and the destruction of the Second Temple have been different?

Saturnine Gout, Sir William Pitt & the American Revolution

The gouty attacks of Sir William Pitt the Elder, the British prime minister, have been speculated to be one contributing factor to the American Revolution.[18,19] Pitt grew up in a wealthy family that delighted in a diet rich in protein and port; this contributed to numerous episodes of gout in both father and son.

Port wines from lead-lined vats in Portugal have previously been shown to contain toxic amounts of lead, explaining the epidemic of saturnine gout among British aristocracy of that era.[17,24] Pitt became a powerful political force and, ultimately, prime minister. He was an outspoken champion of the colonies, believing the American colonies deserved representation with their taxation. Pitt developed an acute episode of gout the night before the vote for the Stamp Act of 1765, stayed home and missed the parliamentary debate; Pitt opposed the act, and historians opine that his influence would have prevailed. The Stamp Act passed and, together with the Tea Act, helped precipitate the American Revolution.[19]

What if … Pitt, who was influential and sympathetic to the colonies, had not had an acute episode of (saturnine) gout on the eve of that fateful parliamentary debate that led to the passing of the Stamp Act? How different might American and British history have been?

See Table 1 (above) for brief comments about gout affecting King Asa, Charles V and dinosaurs.[25-27]

Reactive Arthritis & Columbus

The voyages of Christopher Columbus led to colonization of the New World over 500 years ago. However, during this time Columbus suffered from progressive flares of a debilitating arthritis that were associated with febrile and ocular symptoms, which presumably reflected reactive arthritis.[28]

This was thought to begin during his first voyage, on his return trip to Spain with the Niña and Pinta, in 1493. Columbus wrote that "he had not slept or been able to sleep and hardly had the use of his legs." During his second voyage in 1494, he reportedly became "gravely ill" with "high fever and a drowsiness, so that he lost his sight, memory and all his other senses."[29] Symptoms caused "general disability" and "errors in navigation." Columbus remained ill for almost five months thereafter.[29-31]

On his third voyage, Columbus developed *gotte* (gout, a term then used to refer to rheumatism or arthritis, generally

continued on page 44

FIGURE 1B

Boris M. Joffe, father in-law of one of the authors, Dr. Panush, in the early 1900s, probably on the streets of St. Petersburg, where he was born. He was a protégé of and assistant to Viktor Chernov, leader and theoretician of the socialist-revolutionary anarchist party of Russia. Chernov was minister of agriculture in Alexander Kerensky's Russian Provisional Government and chair of the Russian Constituent Assembly, the duly elected government in the country in a plebiscite held following the fall of the tsardom, lasting until they were deposed by Lenin and the Communists.[37,41]

and non-specifically). Columbus developed lower extremity joint pain, febrile episodes, bilateral eye inflammation, visual changes and pain.[29] At age 51, he was "already an aged man," and by his fourth and final voyage and through his remaining years, he remained largely "paralyzed and bedridden."[32] Columbus' illness is generally considered to have been reactive arthritis.[29]

What if … Columbus had not suffered reactive arthritis that affected and limited his voyages of discovery? How different would modern history have been?

See Table 1 (p. 43) for two more examples of spondyloarthritis: The pharaohs, Moses and the biblical exodus, as well as the Great King Sejong and the golden age of Korean culture.[33-34]

Pain Management, Napoleon & an Epic Defeat at Waterloo

Napoleon, an emperor aspiring to dominate Europe, was invincible until the fateful Battle of Waterloo in 1815.[35] It was Napoleon's military leadership style to awaken early on the mornings of battles and to lead his troops into the fray. Significantly, and unusually, that did not happen at Waterloo. Napoleon rose late in the morning, reportedly spent much of the day napping, off horseback and walking with "difficulty with his legs spread apart," and did not provide his customary leadership.[35,36] Napoleon suffered painful bouts of hemorrhoids.[35] It has been speculated this was likely what happened on the eve of the Battle of Waterloo and that Napoleon was administered sedative analgesics—perhaps narcotics—that impaired his ability to direct his army the following day.

What if … Napoleon hadn't (likely) taken excessive pain medication (likely narcotic) for his thrombosed hemorrhoids on the eve of the epic battle at Waterloo, impairing his leadership and presaging his defeat? How might modern European history have differed?

Royal Hemophilia, Possible Hemophilic Arthropathy, Tsarevich Alexei & the Fall of the Romanov Tsardom

In September 1912, the Russian royal family was vacationing at one of its hunting preserves in the Bialowieza Forest, in what is now eastern Poland, with their five children, including Tsarevich Alexei, the long-awaited heir to the Russian throne.[37] Alexei had hemophilia, inherited from his mother, Alexandra, of Hessian royalty, granddaughter of Queen Victoria, whose descendants carried the gene.[38,39] Alexei fell against an oarlock with an intense pain in his left upper leg and lower abdomen, completely incapacitating him.[40] His condition deteriorated, and he was administered last rites.

The tsarina was a foreigner to the country of her husband, Tsar Nicolas II; she was largely isolated, alone and friendless at the court, trusting few except the dissolute and charismatic monk who had captivated her, Grigori Rasputin. In desperation, Alexandra sent a telegram to Rasputin, to which he responded, "God has seen your tears and heard your prayers. Do not grieve. The Little One will not die. Do not allow the doctors to bother him too much." The bleeding stopped the next day, and Alexei recovered.

Consequently, Rasputin became the tsarina's trusted confidant; surely, if he could save her son's life, he could help her govern Russia while her husband was with his troops at the front during WWI. Russia's entry into the war and the tsarina's interim governance of the nation (with Rasputin's complicity) were disastrous debacles, leading to the fall of the Romanov tsardom.[37]

Events following Nicolas' abdication were complex, with provisional governments, including one led by Alexander Kerensky, deposed by Vladimir Lenin and the Communists in the revolution of October 1917[41] (see Figures 1A–1D).

What if … Tsarevich Alexei did not have a near-fatal episode of hemophilia (possibly with attendant arthropathy) at the royal hunting lodge, leading the tsarina to involve Rasputin in her confounding governance of the country while Nicolas was at the front ("if there had been no Rasputin, there would have been no Lenin" [Alexander Kerensky])? How different might 20th century history have been)?

Possible Giant Cell Arteritis, Hitler & the Rise & Fall of the Third Reich

Adolph Hitler was known to suffer from several medical conditions, possibly including giant cell arteritis (GCA).[42] As a child, he suffered a pulmonary illness, and he was exposed to toxic substances, including mustard gas during World War I.[43] At age 47 he was diagnosed with eczema and dyspepsia.[42]

In 1941, Hitler experienced fatigue, malaise, dizziness, abdominal pain, left temple pain and tenderness, tinnitus, had a systolic blood pressure of 170 mmHg and "coronary insufficiency," diagnosed as vascular spasm and colitis.[42] On July 22, 1942, he developed severe right-sided headaches and unilateral painless vision changes on the right, attributed to coronary sclerosis and vascular spasm. He was treated with intravenous glucose, cold compresses and leeches.[42,43] From 1942 to 1944, Hitler had more than 13 similar attacks.

In 1943, he had a "swollen" temporal artery, recurrent abdominal pain, distension and jaundice, diagnosed as gastritis. Resting tremor and gait abnormalities were diagnosed as Parkinson's disease.[42] In late 1944, Hitler had weight loss, fever and an erythrocyte sedimentation rate of 36 mm/hr and 70 mm/2 hr.[42] March 1944 brought worsening vision (20/80 acuity) and cloudiness of the vitreous body.[43]

The differential diagnosis here is broad and should include vasculitis. Could the symptoms of temporal pain, vision changes, elevated erythrocyte sedimentation rate, weight loss, fevers and perhaps certain others have been GCA? Could Hitler's known amphetamine use have contributed?[42] We suspect the answers are "no" and "no," but the conjecture is not unreasonable. This illustrates the fun of speculating about possible illnesses in historical figures, but also the limitations of the exercise (a comment that generalizes to the entirety of this piece).

What if … Hitler did have giant cell arteritis and could have been treated? How different might that era have been?

Autoimmune Diseases in the White House: Possible Axial Spondyloarthropathy, Autoimmune Polyendocrinopathy Type 2, John F. Kennedy & Presidential Decision Making

John F. Kennedy was our youngest president, 43 years old when he took office. We present him with another president who had autoimmune disease, although his place in history could have been with those having spondyloarthritis (or issues of pain management).

For many years the president's medical records were secret.[44,45] Kennedy was born May 29, 1917. He had a sister with Addison's disease.[46] In 1931, he experienced chronic abdominal symptoms. He also had joint pains, and inflammatory bowel disease was suggested.[44,46] In 1934–35, Kennedy had lymphopenia.[45] His back pain started in adolescence and progressed in the setting of multiple sports injuries.[46,47] He underwent several operations for lumbosacral instability;

FIGURE 1C

Boris M. Joffe (right) and Viktor Chernov (left), New York, c. 1930–40s.

imaging documented alignment and fusion at L5–S1.[47] A clear cause for this was not identified, and he later used crutches.[44,47]

A systolic blood pressure of 80 mmHg was recorded in 1940. Kennedy then had gastrointestinal symptoms and chronic urethritis, for which he took antibiotics.[45] He also experienced episodes of syncope and exhaustion; during a trip to England in September 1947, he was diagnosed with adrenal crisis, returned home and was hospitalized in Boston, where he was treated with desoxycorticosterone acetate and cortisone 25.[48] It was reported he also suffered from complications of malaria.[48]

In 1954, Kennedy had his second back operation and was reported as Case 3 in a journal outlining management of adrenal disease in the perioperative period.[47,48] Unfortunately, his procedure was complicated by severe wound infections, shock and near death, and he remained hospitalized for several months.[44,47] In 1955, he was again hospitalized and started on levothyroxine for treatment of hypothyroidism. Of interest, spinal imaging performed in 1957 demonstrated inflammation at the right sacroiliac joint.[47] Due to the simultaneous diagnosis of hypoadrenalism and hypothyroidism, Kennedy was considered to have had autoimmune polyendocrine syndrome type 2.[48]

In 1961, a list of Kennedy's medications included hydrocortisone, prednisone, methyltestosterone, fludrocortisone, phenobarbital, paregoric (a hydroalcoholic solution containing opium), diphenoxylate, meperidine, methadone, codeine, amphetamines, chlordiazepoxide, meprobamate, methylphenidate and gammaglobulin—a rather formidable menu of medications with the potential to affect cognition.[48]

It has been speculated that he may have suffered from progressive osteoporosis as a result of chronic steroid use.[44] Perhaps Kennedy's back problems directly contributed to his death; a rigid back brace he wore for uncontrolled symptoms kept him upright after the first gunshot at Dallas, which might not have been fatal by itself.[49,50]

Some of the notable events of the Kennedy presidency include the Cuban missile crisis, the Bay of Pigs invasion, the beginning of the Vietnam war, the Berlin airlift, initiation of space exploration, desegregation and civil rights legislation, and the founding of the Peace Corps.

What if … John F. Kennedy had not been symptomatic from autoimmune adrenal insufficiency and inflammatory spine disease, was not consuming a daunting cocktail of analgetic and other mind-altering medications, and did not need to wear a back brace on that fateful day in Dallas? How different might his presidency and the history of those times have been?

Autoimmune Thyroid Disease, Canine Lupus, George H.W. Bush & a Debacle with the Japanese Prime Minister

In 1991, when he was 66, President George H.W. Bush became breathless while jogging. An electrocardiogram demonstrated atrial fibrillation. Later that year he announced he had Graves' disease.[51] He was hospitalized multiple times for uncontrolled symptoms. Interestingly, his wife had the same diagnosis two years earlier, and their son would be diagnosed with ulcerative colitis.[52] The White House dog, Millie, had canine lupus. All of these conditions are considered autoimmune disorders.[53-55]

One possible complication of uncontrolled hyperthyroidism includes flu-like symptoms, such as nausea, fevers and vomiting. It has been speculated that such an episode may have led to Bush's vomiting on the Japanese prime minister at a state dinner in January 1992.[56] Perhaps the perceived weakness of Bush due to chronic illnesses provided an opportunity for the opposing presidential campaign to exploit Bill Clinton's image of youth and vitality.[52]

What if … George H.W. Bush didn't develop hyperthyroidism or had it sufficiently controlled so as to prevent the embarrassing events of the state dinner with the Japanese prime minister? Might his public image have been sufficiently different that he could have been reelected?

Conclusion

We hope this selective presentation of possible instances of rheumatic diseases and related conditions affecting history has been of interest and offered a different perspective and broader appreciation of the connections between illness and historical events. R

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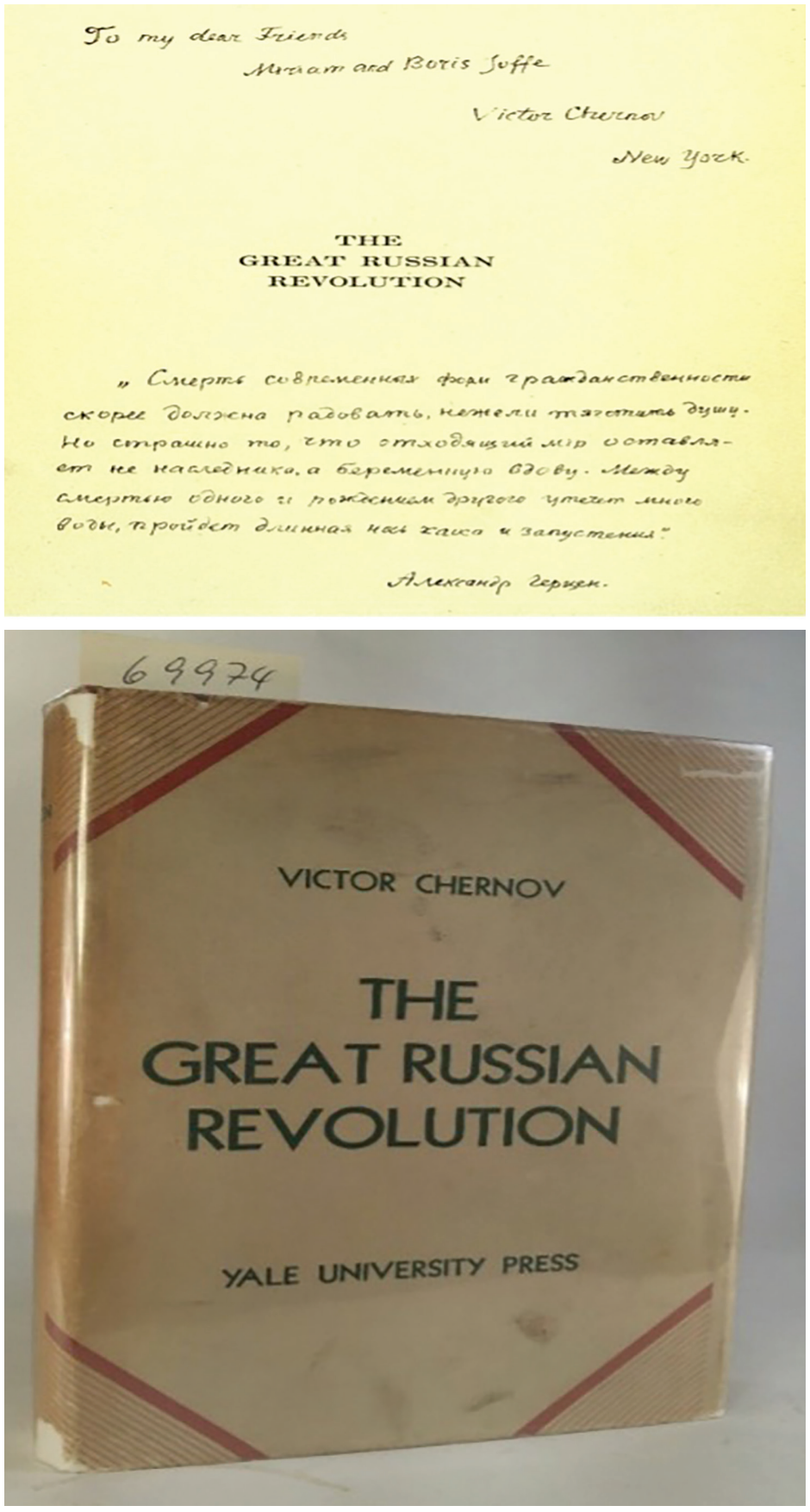
FIGURES 1D AND 1D PT2



Inscription from *The Great Russian Revolution* (1936), given to Miriam and Boris Joffe (in-laws of one of the authors, Dr. Panush) by Viktor Chernov.[41] The inscription translates to: "The death of modern forms of civil society should, perhaps, be something to celebrate rather than to burden our souls. But what is frightening is that the old world leaves behind not an heir, but a pregnant widow. From the death of the former to the birth of the new quite some time will pass—fraught with chaos and desolation." (Attributed to Alexander Herzen, 1812–1870, a Russian socialist ideologue.)

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Advocacy Highlights & Fall Treats

Reflections from the GAC chair

■ **BY ELIZABETH "BLAIR" SOLOW, MD**

I have a special fondness for donuts, although that wasn't always the case. As a child, I found them too sweet. My mother was kind enough to take me to the donut shop early so we could buy some before they were glazed. Over time, I grew to like cake donuts, cinnamon sugar donuts and, now, love the traditional version, although I still scrape off a lot of the sugar. It must be hereditary because my eldest does not really like donuts either—yet. I really appreciate when our nursing team brings donuts in on Friday mornings.

It is the small things that matter. Big numbers like $3.7 *billion*[1] in lobbying money or 10,000 bills introduced in the 117th Congress[2,3] seem overwhelming and can get in the way of the things that matter more—the impacts on our practices and patients—which brings me back to donuts. Although the donuts do help my morale, they are probably not the healthiest way to prevent burnout.[4]

Advocacy may be one avenue that can help. What does it mean to lobby Congress? How will that help someone feel more empowered or experience less moral distress? During my tenure as chair of the ACR's Government Affairs Committee (GAC), I've learned about the topsy-turvy rhythm of government, the role of lobbying firms, how laws are made and then interpreted on the administration side. Most importantly, I've learned that even a small voice—with persistence—can effect change over time. To some degree I'm preaching to the choir because you're already reading this article, and maybe you like donuts, too. My hope is you will take this to heart and talk to your friends and colleagues about how advocacy can make a difference in the way we practice medicine and the way that we're able to take care of our patients. We need much larger numbers lending their voices in small ways to help effect change.

Advocacy Highlights from 2022

We recently returned from lobbying Congress in September during our annual Advocates for Arthritis Hill Day, focusing on two main issues: step therapy and copay accumulator programs. In collaboration with the Committee on Research, we also met with the leadership team at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) on strategic research goals and funding opportunities for rheumatology researchers.

In my final update to you as GAC chair, I highlight several areas of active efforts with results to date.

Reimbursement: Medicare cuts are looming. We expect a 2.75% cut, plus possibly a PAYGO 4% cut to go live on Jan. 1, 2023, unless Congress legislates a fix to avoid those cuts, such as HR 8800.

The 2023 proposed rule for the Medicare Physician Fee Schedule (PFS) included major cuts to ultrasound reimbursement, but intact valuation of evaluation and management services (E/M). Unfortunately, although not unexpectedly, additional cuts to reimbursement were proposed. We have sent letters to the Centers for Medicare & Medicaid Services and are fighting back with other coalitions and the American Medical Association (AMA). We are shifting our advocacy focus to reform the PFS in line with the AMA and other specialties.

Utilization management: This may be the ultimate pain, requiring at times a very fine donut fix. Prior authorization and step therapy legislation is in both the Senate and the House, and we are hoping to get the bills across the finish line. The prior authorization bill passed in the House, so we are hopeful.

We are monitoring the FTC investigation into pharmacy benefit manager (PBM) practices closely. We have been working on Medicare downcoding with the ACR Insurance Subcommittee of the Committee on Rheumatologic Care. Robust activity at the state level targeting these issues has been ongoing.

Research funding: Arthritis research funding from the Department of Defense was stalled this year due to budget and administrative hurdles. We are closer to this resource than before and hope that next year we can inch closer.

Pandemic: The public health emergency (PHE) was extended yet again, although we expect this to be the last time. We have supported telehealth provisions in the PFS, and legislation has extended flexibilities well into 2023. Further advocacy will be needed to maintain this resource for patients.

Reproductive healthcare: The Supreme Court ruling on *Dobbs* overturning Roe v. Wade has had profound impacts on our delivery of patient care. The ACR government affairs team is tracking federal, administrative (HHS, FDA) and state conversations around these substantial impacts and the next steps for rheumatology physicians and interprofessional team members.

Drug pricing: The passed Inflation Reduction Act includes provisions that allow Medicare to negotiate drug pricing for the most expensive medications. This is an enormous shift in policy that can impact the cost of drugs in the U.S.

If you made it this far, you care a lot, too. Head over to RheumPAC to invest in our seat at the table. To lend your voice, send a pre-written letter to your members of Congress from the Legislative Action Center (**https://www.rheumatology.org/Advocacy/Legislative-Action-Center**), and encourage others to do so.

Thank you as always to the hard-working GAC members, whose invaluable insights guides our agenda, and to our ACR staff team of extraordinary people who care a lot about how to make healthcare better.

Wishing you a happy holiday season, and maybe an apple cider donut or two. **R**

Elizabeth "Blair" Solow, MD, is the outgoing chair of the Government Affairs Committee for the ACR and an assistant professor of medicine in the Division of Rheumatic Diseases at UT Southwestern Medical Center, Dallas.

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Ongoing Advocacy Efforts Seek Use of Complex Administration Codes for Biologics

■ **FROM THE COLLEGE**

The ACR and other advocacy organizations continue to work with the Centers for Medicare & Medicaid Services (CMS) to advocate for appropriate reimbursement of the administration of complex biologic therapies.

Over the past several years, Medicare Administrative Contractors (MACs) have implemented Local Coverage Articles (LCAs) prohibiting the use of the chemotherapy administration codes (CPT 96401–96549) when coding for the administration of certain complex biologic drugs, instead requiring use of the diagnostic or therapeutic codes (CPT 96360–96379). The ACR has spoken with leaders from each of the MACs; however, they are unyielding in their opinion that this policy is accurate and appropriate.

In June, the ACR led a multispecialty sign-on letter asking the CMS to review the policymaking process used to implement these policy changes. The ACR was joined by nine other specialty societies in arguing that the MACs are using LCAs to bypass the more rigorous Local Coverage Determination process and subvert the transparency and stakeholder engagement intended by the 21st Century Cures Act. The letter asks the CMS to invalidate all current LCAs that restrict coverage or patient access.

In its response, the CMS acknowledged the concerns raised and suggested this specific issue may fall under the purview of its Center for Program Integrity (CPI). The ACR has subsequently reached out to the CPI and will pursue additional opportunities for dialogue.

For questions or additional information, contact **practice@rheumatology.org**. **R**

Reading Rheum

Research from *AC&R* Encapsulated

MoCA as a Screening Test in SLE

Assessing the utility of the Montreal Cognitive Assessment (MoCA)

■ **BY OSHRAT E. TAYER-SHIFMAN, MD, KIMBERLEY YUEN, BSc, MD, & ZAHI TOUMA, MD, PhD, FACP, FACR**

Why was this study done? Cognitive impairment is a common manifestation of systemic lupus erythematosus (SLE), with a prevalence of 40% based on objective measures. The ACR Neuropsychological Battery (ACR-NB) is the gold standard test for cognitive impairment screening and diagnosis in adult SLE patients; however, it is not widely available. The Montreal Cognitive Assessment (MoCA) was developed to screen for neurocognitive disorder in the older population, but no evidence exists of its validity to accurately identify cognitive impairment in patients with SLE. We studied the utility of the MoCA as a screening test for cognitive impairment compared with the ACR-NB.

What were the study methods? Two hundred and eighty-five adults with SLE were administered the ACR-NB and the MoCA. For the ACR-NB, patients were classified as cognitively impaired with a Z-score of ≤-1.5 in two or more domains. The area under the curve (AUC) and sensitivities/specificities were determined. A discriminant function analysis was also applied.

What were the key findings? Cognitive impairment was not accurately identified by the MoCA, compared with the ACR-NB (AUC of 0.66). Sensitivity and specificity were poor, at 50% and 69%, respectively for the MoCA recommended cutoff of 26, and 80% and 45%, respectively for a higher cutoff of 28. The discriminant function analysis demonstrated low ability of the MoCA to identify different cognitive impairment status.

What were the main conclusions? This large study evaluated the MoCA as a screening test for cognitive impairment in patients with SLE. Compared with the ACR-NB, the MoCA failed to show the sensitivity and specificity needed.

What are the implications for patients and clinicians? When screening for cognitive impairment in patients with SLE, the healthcare team should use a test that has evidence for validity in SLE. The MoCA can neither diagnose cognitive impairment nor rule out cognitive impairment in patients with SLE. The low specificity of the MoCA may lead to overdiagnosis and concern among patients. We have shown in a previous work that the Automated Neuropsychological Assessment Metrics (ANAM) can be used to screen for cognitive impairment in SLE.[1]

The study: Tayer-Shifman OE, Yuen K, Green R et al. Assessing the utility of the Montreal Cognitive Assessment (MoCA) in screening for cognitive impairment in patients with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2022 Jun 22. Online ahead of print.

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Cumulative Social Disadvantage

A cross-sectional analysis of the National Survey of Children's Health

■ **BY WILLIAM DANIEL SOULSBY, MD**

Why was this study done? Health disparities in juvenile idiopathic arthritis (JIA) are poorly understood. Existing studies examine social determinants of health as independent risk factors, although we hypothesize increased exposure to social disadvantage may be associated with higher risk. Combined scoring systems have been used to investigate social determinants in diseases, such as hypertension and diabetes. We investigated the role of cumulative social disadvantage on childhood arthritis diagnoses, as well as severity of disease.

What were the study methods? A cross-sectional analysis was performed across four years of the National Survey of Children's Health (NSCH)—a nationally representative survey examining child health across the U.S. A cumulative social disadvantage score was created on the basis of existing proposed risk factors in JIA, including adverse childhood experiences, poverty, public or lack of insurance, and guardian education. This score was used to analyze the association with childhood arthritis among all survey respondents, as well as moderate-to-severe disease among those with reported arthritis.

What were the key findings? Cumulative social disadvantage was associated with a childhood arthritis diagnosis, highest among those with exposure to all four social variables with an adjusted odds ratio (aOR) of 12.4 (95% confidence interval [95% CI] 2.9–53.3). It was also associated with moderate-to-severe disease, also highest for those with the highest score of 4, with an aOR of 12.4 (95% CI 1.8–82.6).

What were the main conclusions? Cumulative social disadvantage is associated with childhood arthritis diagnoses among a nationally representative sample of U.S. children and associated with increased disease severity, suggesting the presence of a social gradient in childhood arthritis.

What are the implications for patients? Children with increased exposure to social disadvantage may have higher odds of having arthritis and may have higher disease severity.

What are the implications for clinicians? Our findings suggest that implementation of social disadvantage screening in the pediatric rheumatology clinic may have the potential to identify patients at risk for higher disease severity who may benefit from targeted services, such as patient navigation programs and social services.

The study: Soulsby WD, Lawson E, Pantell MS. Cumulative social disadvantage is associated with childhood arthritis: A cross-sectional analysis of the National Survey of Children's Health. *Arthritis Care Res (Hoboken)*. 2022 Jul 29. Epub ahead of print.

Surgical Weight Loss Interventions

Their cost effectiveness for patients with knee OA & class III obesity

■ **BY ALEKSANDRA KOSTIC, BSE, VALIA LEIFER, BA, & ELENA LOSINA, PhD, MSC**

Why was this study done? Weight loss can alleviate knee osteoarthritis (OA) related pain for patients with knee OA and obesity. However, current knee OA treatment guidelines do not address weight loss strategies other than diet and exercise. Bariatric surgery can yield substantial, sustainable weight loss among individuals with class III obesity (BMI ≥40 kg/m^2), but its value for patients with knee OA is uncertain due to concerns about cost, efficacy and adverse events.

What were the study methods? We used the Osteoarthritis Policy Model (OAPol) to evaluate the effects of Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) bariatric surgery on lifetime costs and quality of life in patients with class III obesity and moderate knee OA. Each bariatric surgery strategy was considered in conjunction with usual knee OA care, which consisted of nonsteroidal anti-inflammatory drugs, physical therapy, intra-articular corticosteroid injections, tramadol, oxycodone, total knee replacement and revision total knee replacement. We calculated incremental cost-effectiveness ratios (ICERs), discounted at 3% per year, which represent the difference in lifetime costs to the difference in quality adjusted life years (QALYs) between the two treatment strategies. We performed sensitivity analyses to evaluate the effect of uncertainty in model inputs on results.

What were the key findings? Compared with usual care only, both RYGB and LSG reduced opioid utilization and increased total knee replacement (TKR) utilization. LSG yielded less benefit at a higher cost than RYGB (most likely due to lower and less sustainable weight loss). RYGB yielded a very favorable ICER ($5,300/QALY).

What were the main conclusions? Bariatric surgery provides substantial weight loss and other clinical benefits. Our results suggest RYGB offers a better value than LSG for a population with class III obesity and knee OA.

What are the implications for patients? Patients with class III obesity and knee OA may consider bariatric surgery to alleviate knee OA-related symptoms. They should discuss the risks and benefits of different weight loss strategies with their providers.

What are the implications for clinicians? Patients with class III obesity and moderate knee OA may benefit from bariatric surgery, which may reduce future opioid use. It is reasonable to discuss bariatric surgery as a weight loss strategy with this patient population.

The study: Kostic AM, Leifer VP, Gong Y, et al. The cost-effectiveness of surgical weight loss interventions for patients with knee osteoarthritis and class III obesity. *Arthritis Care Res (Hoboken)*. 2022 Jun 3. Epub ahead of print. R

The Pediatric Rheumatology Workforce

Too many kids, too few providers

■ BY KERI LOSAVIO

"Fifty percent of kids with rheumatic disease are taken care of by adult providers," says Jay J. Mehta, MD, MS, attending physician and fellowship program director, Department of Rheumatology, Children's Hospital of Philadelphia, and a co-author of the ACR's recent pediatric workforce shortage study.[1,2] "But adult rheumatologists may not have specific training in the rheumatic conditions that uniquely affect children or in the unique physical and psychosocial aspects of chronic disease in childhood. They may not have knowledge of medication dosing in children and could under- or overtreat as a consequence.

DR. MEHTA

"Additionally, the wait times for some of these pediatric rheumatologists can be months. Arthritis can cause significant growth issues within months. Untreated lupus can cause kidney failure within months," he continues.

These are the very real consequences of the situation that currently exists: The U.S. has too few pediatric rheumatologists to care for the number of children who need care for rheumatic conditions—*and that gap is only expected to get worse.*

The Scope of the Problem

Similar to workforce shortages in adult rheumatology, shortages in the pediatric rheumatology workforce have long been a concern. A 2006 study by the American Board of Pediatrics reported a total of 200 board-certified pediatric rheumatologists in the U.S., with only three pediatric rheumatologists per million children and none practicing in 14 states.[3]

In 2007, Sacks et al. estimated that nearly 300,000 children in the U.S. have significant pediatric arthritis and other rheumatic conditions. The researchers' estimate of the annualized number of ambulatory healthcare visits was 827,000.[4]

An ACR U.S. rheumatology workforce study report on the supply and demand of rheumatologists from 2005–25 projected the demand for pediatric rheumatologists in 2025 would exceed the supply by 191 pediatric providers.[5]

The ACR's report on the pediatric rheumatology workforce states that the pediatric rheumatology workforce in 2015 was estimated at 287 full-time equivalent (FTE) pediatric providers, while the estimated excess demand was 95 providers (33%). Correll et al. state: "The projected demand will continue to increase to almost 100% (n=230) by 2030 if no changes occur in succession planning, new graduate entrants into the profession and other factors associated with the workforce."[1]

DR. CORRELL

Colleen K. Correll, MD, MPH, assistant professor in the Division of Pediatric Rheumatology at the University of Minnesota Medical School, Minneapolis, and the corresponding author for the recent study, says the current shortage and future projections of a workforce shortage for pediatric rheumatologists come as no surprise to providers and patients alike.

"Most of us [pediatric rheumatologists] feel the impact of the workforce shortage on a daily basis when we practice clinical medicine," she says, citing, for example, the long wait times to see new patients.

Long wait times to see a provider cause stress and anxiety for patients, particularly new ones, and can sometimes result in worsening disease, says Dr. Correll. For established patients, scheduling timely follow-up appointments can be challenging.

Because so many states have no pediatric rheumatologists and in others the only pediatric providers are in large urban areas, distance complicates scheduling and timely access to care. For example, all new and return English-speaking parents/guardians of patients visiting a single center in Minneapolis were surveyed over a period of six weeks to assess barriers to care. In this study, Bullock et al. found that 28% of the parents (45/159) reported traveling more than three hours to the pediatric rheumatology clinic. Forty-three percent (65/152) reported travel as inconvenient.[6]

Thus, patients and rheumatologists face a twofold and growing problem: there are too few pediatric rheumatology providers to care for the growing number of children with rheumatic conditions, and significant areas of the country have no pediatric rheumatologists at all.

Closing the Gap

Closing the gap between the number of providers and the number of children in need of care will take some creative solutions.

"The challenge is how many people are coming into the field every year," says Dr. Mehta. "There are only about 20 matched fellows each year, meaning 20 people are entering the workforce. If there were no retirement, then we wouldn't close the gap for over 11 years. The problem is that there is a significant number of retirees every year, so we are unlikely to close that gap."

Although residents and fellows trained in adult rheumatology receive some training in pediatric rheumatologic diseases, the training and exposure is minimal and not nearly sufficient to understand the complexities of pediatric rheumatologic health.

"Many medical students don't know that rheumatic disease in children is a specialty," he says. "If you're not exposed to the specialty, then you don't have role models."

Given the particular and wide-ranging effects of rheumatologic diseases on children, Dr. Mehta says rheumatologists specifically trained in pediatric rheumatology are necessary to truly provide optimal care for these children. "There are lots of differences in not only how the disease themselves affect children vs. adults," he says, "but also in complications over time."

He notes that children are greatly affected physically, as well as socially, by arthritis and other rheumatic diseases. The conditions often limit a child's ability to run and play, and interrupt school schedules and education. Their endocrine and reproductive systems may be affected. "All of a child's developing organs could be affected by autoimmune disease," he says.

By 2030, an estimated 142% increase in fellowship slots for pediatric rheumatologists will be needed to meet demand. However, unlike in adult rheumatology programs in which 100 residents go unmatched each year, the challenge in pediatric rheumatology is to increase the interest in, and demand for, available fellowship slots.

Solutions to help increase the supply of providers include increasing recruitment of physician and nonphysician providers, such as physician assistants and nurse practitioners to pediatric rheumatology; increasing the number of fellowships in underserved areas; using telemedicine; and working with healthcare partners in the community (e.g., primary care providers, occupational and physical therapists) to provide comprehensive patient care.

These solutions are all identified in an ACR workforce solutions initiative to help address ways to close the gap between supply and demand of rheumatologists. Described in detail in an article in *The Rheumatologist*, the initiative first focuses on targeting the above solutions to areas in geographical areas in the U.S. in most need, specifically the South and Southwest.[1,7]

"The specialty really has to focus on optimizing initiatives that have already begun, supporting those initiatives to help them grow and developing creative new solutions," says Dr. Correll. **R**

Keri Losavio is the editor of *The Rheumatologist*.

References

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7. Nierengarten MB. The ACR launches initiative to tackle workforce shortage. *The Rheumatologist*. 2022 May 12.

INDICATION

Rheumatoid Arthritis

- XELJANZ®/XELJANZ® XR (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers.
- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic disease-modifying antirheumatic drugs (DMARDs) or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with XELJANZ* 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 XELJANZ 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 XELJANZ use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Avoid use of XELJANZ in patients with an active, serious infection, including localized infections.

In the UC† population, XELJANZ 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

The risks and benefits of treatment with XELJANZ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection, or those who have lived or traveled in areas of endemic TB or mycoses. Viral reactivation including herpes virus and hepatitis B reactivation have been reported. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infection.

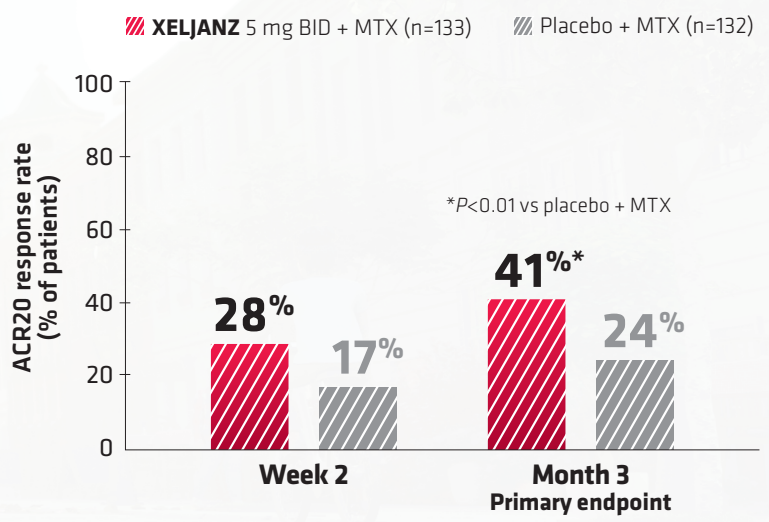
MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular (CV) risk factor comparing XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden CV death, was observed with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day. A XELJANZ 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA‡.
For UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

*Unless otherwise stated, "XELJANZ" in the Important Safety Information refers to XELJANZ, XELJANZ XR, and XELJANZ Oral Solution.
†UC=ulcerative colitis. XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active UC, who have had an inadequate response or intolerance to one or more TNF blockers. Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
‡PsA=psoriatic arthritis. XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
ACR=American College of Rheumatology; BID=twice daily; DAS28-4(ESR)=Disease Activity Score for 28-joint counts based on erythrocyte sedimentation rate (4 variables); HAQ-DI=Health Assessment Questionnaire–Disability Index; hsCRP=high-sensitivity C-reactive protein; IR=inadequate responder; MTX=methotrexate; RA=rheumatoid arthritis; TNF=tumor necrosis factor.

XELJANZ DELIVERED A RAPID AND POWERFUL RESPONSE[1-3,a]

ORAL Step in TNF Blocker-IR Patients[1-3] | ACR20



As early as week 2:
Reduction in signs and symptoms of RA (higher ACR20) vs placebo[1-3,a]

[a]Nonresponder imputation was applied to missing sign/symptom data.[2]

XELJANZ contains a **BOXED WARNING** for Serious Infections, Mortality, Malignancies, Major Adverse Cardiovascular Events, and Thrombosis.[1]

Study design for ORAL Step: A 6-month, randomized, double-blind, placebo-controlled, multicenter trial in which 399 patients with moderately to severely active RA who had an inadequate response to ≥1 approved TNF blocker (patients were also MTX-IR) received XELJANZ 5 mg BID or 10 mg BID (XELJANZ 10 mg BID is not approved for RA) or placebo (all patients on stable background MTX). Stable low-dose oral glucocorticoids allowed, as were stable doses of antimalarial agents (XELJANZ 5 mg 9%; placebo 4%). At 3 months, all placebo patients were advanced blindly to XELJANZ 5 mg or 10 mg BID (with background MTX). **The 3 coprimary endpoints were ACR20 response rate, HAQ-DI change, and rate of DAS28-4(ESR) <2.6 at month 3. Nonresponder imputation was applied to missing sign/symptom data.[1,3]**

ACR20 response is defined as improvements of 20% or more from baseline in the number of tender/painful and swollen joints and in at least 3 of the following domains: Patient's Global Assessment of arthritis, Physician's Global Assessment of arthritis, Patient's Assessment of Arthritis Pain, disability as measured by the HAQ-DI, or hsCRP level.[4,5]

IMPORTANT SAFETY INFORMATION (cont'd)

MALIGNANCIES

Malignancies, including lymphomas and solid tumors, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day compared with TNF blockers.

Lymphoma and lung cancers were observed at a higher rate in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with XELJANZ, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy while on treatment, and patients who are current or past smokers. A XELJANZ 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

Other malignancies were observed in clinical studies and the postmarketing setting including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer. NMSCs have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

RA patients 50 years of age and older with at least one CV risk factor, treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily, had a higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue XELJANZ 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 XELJANZ, particularly in patients who are current or past smokers and patients with other CV risk factors. Inform patients about the symptoms of serious CV events. A XELJANZ 10 mg twice a day (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

Please see additional Important Safety Information and brief summary of full Prescribing Information, including **BOXED WARNING**, on the following pages.

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IMPORTANT SAFETY INFORMATION (cont'd)

THROMBOSIS

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one CV risk factor treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid XELJANZ in patients at risk. Discontinue XELJANZ and promptly evaluate patients with symptoms of thrombosis.

A XELJANZ 10 mg twice daily (or XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA. In a long-term extension study in UC, five cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one death in a patient with advanced cancer. For UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in XELJANZ clinical trials, although the role of JAK inhibition is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). There was no discernible difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids. XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs).

HYPERSENSITIVITY

Angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving XELJANZ and some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction.

LABORATORY ABNORMALITIES

Lymphocyte Abnormalities: Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts. Avoid initiation of XELJANZ treatment in patients with a count less than 500 cells/mm^3. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, treatment with XELJANZ is not recommended. Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Monitor lymphocyte counts at baseline and every 3 months thereafter.

Neutropenia: Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. Avoid initiation of XELJANZ treatment in patients with an ANC less than 1000 cells/mm^3. For patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with XELJANZ is not recommended. Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia: Avoid initiation of XELJANZ treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment. Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

References: 1. XELJANZ [prescribing information]. New York, NY: Pfizer Inc., January 2022. **2.** Data on file. Pfizer Inc., New York, NY. **3.** Burmester GR, Blanco R, Charles-Schoeman C, et al; ORAL Step Investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381(9865):451-460. **4.** Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med*. 2017;377(16):1537-1550. **5.** Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med*. 2017;377(16):1525-1536.

Please see brief summary of full Prescribing Information, including **BOXED WARNING**, on the following pages.

Liver Enzyme Elevations: Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. If drug-induced liver injury is suspected, the administration of XELJANZ should be interrupted until this diagnosis has been excluded. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury.

Lipid Elevations: Treatment with XELJANZ was associated with dose-dependent increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. Manage patients with hyperlipidemia according to clinical guidelines. Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ therapy.

VACCINATIONS

Avoid use of live vaccines concurrently with XELJANZ. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy.

PATIENTS WITH GASTROINTESTINAL NARROWING

Caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended-release formulation.

HEPATIC and RENAL IMPAIRMENT

Use of XELJANZ in patients with severe hepatic impairment is not recommended. For patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily, reduce to XELJANZ 5 mg once daily. For UC patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 10 mg twice daily, reduce to XELJANZ 5 mg twice daily. If taking XELJANZ XR 22 mg once daily, reduce to XELJANZ XR 11 mg once daily.

ADVERSE REACTIONS

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials in patients with RA with XELJANZ 5 mg twice daily and placebo, respectively, (occurring in greater than or equal to 2% of patients treated with XELJANZ with or without DMARDs) were upper respiratory tract infection, nasopharyngitis, diarrhea, headache, and hypertension. The safety profile observed in patients with active PsA treated with XELJANZ was consistent with the safety profile observed in RA patients.

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials for UC were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

USE IN PREGNANCY

Available data with XELJANZ use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy. In animal studies, tofacitinib at 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. The relevance of these findings to women of childbearing potential is uncertain. Consider pregnancy planning and prevention for females of reproductive potential.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION.
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

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

SERIOUS INFECTIONS Patients treated with XELJANZ* 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 XELJANZ 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 XELJANZ use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with XELJANZ 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 XELJANZ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

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 XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day. A XELJANZ/XELJANZ Oral Solution 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

MALIGNANCIES Malignancies, including lymphomas and solid tumors, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day compared with TNF blockers.

Lymphomas and lung cancers were observed at a higher rate in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

MAJOR ADVERSE CARDIOVASCULAR EVENTS RA patients 50 years of age and older with at least one cardiovascular risk factor, treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue XELJANZ in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid XELJANZ in patients at risk. Discontinue XELJANZ and promptly evaluate patients with symptoms of thrombosis.

INDICATIONS AND USAGE

Rheumatoid Arthritis XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic disease-modifying antirheumatic drugs (DMARDs) or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ankylosing Spondylitis XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Polyarticular Course Juvenile Idiopathic Arthritis XELJANZ/XELJANZ Oral Solution is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of XELJANZ/XELJANZ Oral Solution in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

CONTRAINDICATIONS

None.

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 XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

In the UC population, XELJANZ treatment with 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Additionally, opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Avoid use of XELJANZ in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ 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.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. XELJANZ should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections.

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are recommended.

Tuberculosis Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ.

Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ.

Viral Reactivation Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. Postmarketing cases of hepatitis B reactivation have been reported in patients treated with XELJANZ. The impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ. The risk of herpes zoster is increased in patients treated with XELJANZ and appears to be higher in patients treated with XELJANZ in Japan and Korea.

Mortality Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day had a higher observed rate of all-cause mortality, including sudden cardiovascular death, compared to those treated with TNF blockers in a large, randomized, postmarketing safety study (RA Safety Study 1). The incidence rate of all-cause mortality per 100 patient-years was 0.88 for XELJANZ 5 mg twice a day, 1.23 for XELJANZ 10 mg twice a day, and 0.69 for TNF blockers. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with XELJANZ.

A XELJANZ/XELJANZ Oral Solution 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA, PsA, or AS.

For the treatment of UC, use XELJANZ/XELJANZ XR at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

Malignancy and Lymphoproliferative Disorders Malignancies, including lymphomas and solid cancers, were observed in clinical studies of XELJANZ.

In RA Safety Study 1, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day as compared with TNF blockers. The incidence rate of malignancies (excluding NMSC) per 100 patient-years was 1.13 for XELJANZ 5 mg twice a day, 1.13 for XELJANZ 10 mg twice a day, and 0.77 for TNF blockers. Patients who are current or past smokers are at additional increased risk.

Lymphomas and lung cancers, which are a subset of all malignancies in RA Safety Study 1, were observed at a higher rate in patients treated with XELJANZ 5 mg twice a day and XELJANZ 10 mg twice a day compared to those treated with TNF blockers. The incidence rate of lymphomas per 100 patient-years was 0.07 for XELJANZ 5 mg twice a day, 0.11 for XELJANZ 10 mg twice a day, and 0.02 for TNF blockers. The incidence rate of lung cancers per 100 patient-years among current and past smokers was 0.48 for XELJANZ 5 mg twice a day, 0.59 for XELJANZ 10 mg twice a day, and 0.27 for TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with XELJANZ, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy while on treatment, and patients who are current or past smokers. A XELJANZ/XELJANZ Oral Solution 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

In Phase 2B, controlled dose-ranging trials in *de-novo* renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

Other malignancies were observed in clinical studies and the postmarketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

Non-Melanoma Skin Cancer Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

Major Adverse Cardiovascular Events In RA Safety Study 1, RA patients who were 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily had a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke, compared to those treated with TNF blockers. The incidence rate of MACE per 100 patient-years was 0.91 for XELJANZ 5 mg twice a day, 1.11 for XELJANZ 10 mg twice a day, and 0.79 for TNF blockers. The incidence rate of fatal or non-fatal myocardial infarction per 100 patient-years was 0.36 for XELJANZ 5 mg twice a day, 0.39 for XELJANZ 10 mg twice a day, and 0.20 for 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 XELJANZ, 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 XELJANZ in patients that have experienced a myocardial infarction or stroke. A XELJANZ/XELJANZ Oral Solution 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

*Unless otherwise stated, "XELJANZ" in the brief summary refers to XELJANZ, XELJANZ XR, and XELJANZ Oral Solution.

Thrombosis Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis, have occurred in patients treated with XELJANZ and other Janus kinase (JAK) inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death.

Patients with rheumatoid arthritis 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ at both 5 mg or 10 mg twice daily compared to TNF blockers in RA Safety Study 1 had an observed increase in incidence of these events. The incidence rate of DVT per 100 patient-years was 0.22 for XELJANZ 5 mg twice a day, 0.28 for XELJANZ 10 mg twice a day, and 0.16 for TNF blockers. The incidence rate of PE per 100 patient-years was 0.18 for XELJANZ 5 mg twice a day, 0.49 for XELJANZ 10 mg twice a day, and 0.05 for TNF blockers.

A XELJANZ/XELJANZ Oral Solution 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA, PsA, or AS.

In a long-term extension study in patients with UC, five cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one death in a patient with advanced cancer.

Promptly evaluate patients with symptoms of thrombosis and discontinue XELJANZ in patients with symptoms of thrombosis.

Avoid XELJANZ in patients that may be at increased risk of thrombosis. For the treatment of UC, use XELJANZ/XELJANZ XR at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

Gastrointestinal Perforations Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ, although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Hypersensitivity Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving XELJANZ/XELJANZ XR. Some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction.

Laboratory Abnormalities

Lymphocyte Abnormalities Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean absolute lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections.

Avoid initiation of XELJANZ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).

In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, treatment with XELJANZ is not recommended.

Monitor lymphocyte counts at baseline and every 3 months thereafter.

Neutropenia Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo.

Avoid initiation of XELJANZ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3).

For patients who develop a persistent ANC of 500 to 1000 cells/mm^3, interrupt XELJANZ dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with XELJANZ is not recommended.

Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia Avoid initiation of XELJANZ treatment in patients with a low hemoglobin level (i.e., less than 9 g/dL). Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.

Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Liver Enzyme Elevations Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy.

Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ should be interrupted until this diagnosis has been excluded.

Lipid Elevations Treatment with XELJANZ was associated with dose-dependent increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ therapy.

Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Vaccinations Avoid use of live vaccines concurrently with XELJANZ. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

A patient experienced dissemination of the vaccine strain of varicella zoster virus, 16 days after vaccination with live attenuated (Zostavax) virus vaccine and 2 days after treatment start with tofacitinib 5 mg twice daily. The patient was varicella virus naïve, as evidenced by no previous history of varicella infection and no anti-varicella antibodies at baseline. Tofacitinib was discontinued and the patient recovered after treatment with standard doses of antiviral medication.

Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy.

Risk of Gastrointestinal Obstruction with a Non-Deformable Extended-Release Formulation such as XELJANZ XR

As with any other non-deformable material, caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended release formulation.

ADVERSE REACTIONS

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

- Serious Infections
- Mortality
- Malignancy and Lymphoproliferative Disorders
- Major Adverse Cardiovascular Events
- Thrombosis
- Gastrointestinal Perforations
- Hypersensitivity
- Laboratory Abnormalities

Clinical Trials Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Rheumatoid Arthritis The clinical studies described in the following sections were conducted using XELJANZ. Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily. The recommended dose for XELJANZ XR is 11 mg once daily. A dosage of XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not a recommended regimen for the treatment of rheumatoid arthritis. In RA Safety Study 1, 1455 patients were treated with XELJANZ 5 mg twice daily, 1456 patients were treated with 10 mg twice daily, and 1451 patients were treated with a TNF blocker for a median of 4.0 years.

The following data includes two Phase 2 and five Phase 3 double-blind, placebo-controlled, multicenter trials. In these trials, patients were randomized to doses of XELJANZ 5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, XELJANZ 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven placebo-controlled protocols included provisions for patients taking placebo to receive treatment with XELJANZ at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore, some analyses that follow include patients who changed treatment by design or by patient response from placebo to XELJANZ in both the placebo and XELJANZ group of a given interval. Comparisons between placebo and XELJANZ were based on the first 3 months of exposure, and comparisons between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily were based on the first 12 months of exposure.

The long-term safety population includes all patients who participated in a double-blind, placebo-controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of XELJANZ doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose.

The most common serious adverse reactions were serious infections.

The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking XELJANZ and 3% for placebo-treated patients.

Overall Infections

In the seven placebo-controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group.

The most commonly reported infections with XELJANZ were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

Serious Infections In the seven placebo-controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily XELJANZ group minus placebo.

In the seven placebo-controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection.

Tuberculosis In the seven placebo-controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven placebo-controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of XELJANZ and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days).

Opportunistic Infections (excluding tuberculosis) In the seven placebo-controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven placebo-controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days).

Malignancy

In the seven placebo-controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-years) who received either XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily XELJANZ group minus placebo.

In the seven placebo-controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with XELJANZ 10 mg twice daily.

The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma.

Laboratory Abnormalities

Lymphopenia In the placebo-controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections.

Neutropenia In the placebo-controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group.

There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the placebo-controlled clinical trials.

Liver Enzyme Elevations Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with XELJANZ. In patients experiencing liver enzyme elevation,

modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalization of liver enzymes.

In the placebo-controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and XELJANZ 5 mg, and 10 mg twice daily groups.

In the placebo-controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

One case of drug-induced liver injury was reported in a patient treated with XELJANZ 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

Lipid Elevations In the placebo-controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the placebo-controlled clinical trials are summarized below:

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 10% in the XELJANZ 5 mg twice daily arm and 12% in the XELJANZ 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ-treated patients.

In a placebo-controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the placebo-controlled clinical trials.

Serum Creatinine Elevations In the placebo-controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 5 mg twice daily or 10 mg twice daily XELJANZ and at least 1% greater than that observed in patients on placebo with or without DMARD are summarized in the following table.

Common Adverse Reactions* in Clinical Trials of XELJANZ for the Treatment of Rheumatoid Arthritis With or Without Concomitant DMARDs (0-3 Months)

Preferred Term	XELJANZ 5 mg Twice Daily N = 1336 (%)	XELJANZ 10 mg Twice Daily** N = 1349 (%)	Placebo N = 809 (%)
Upper respiratory tract infection	4	4	3
Nasopharyngitis	4	3	3
Diarrhea	4	3	2
Headache	4	3	2
Hypertension	2	2	1

N reflects randomized and treated patients from the seven placebo-controlled clinical trials.

* reported in ≥2% of patients treated with either dose of XELJANZ and ≥1% greater than that reported for placebo.

** the recommended dose of XELJANZ for the treatment of rheumatoid arthritis is 5 mg twice daily.

Other adverse reactions occurring in placebo-controlled and open-label extension studies included:

Blood and lymphatic system disorders: Anemia

Infections and infestations: Diverticulitis

Metabolism and nutrition disorders: Dehydration

Psychiatric disorders: Insomnia

Nervous system disorders: Paresthesia

Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)

Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea

Hepatobiliary disorders: Hepatic steatosis

Skin and subcutaneous tissue disorders: Rash, erythema, pruritus

Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling

Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers

General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

Clinical Experience in Methotrexate-Naïve Patients

Study RA-VI was an active-controlled clinical trial in methotrexate-naïve patients. The safety experience in these patients was consistent with Studies RA-I through V.

Psoriatic Arthritis XELJANZ 5 mg twice daily and 10 mg twice daily were studied in 2 double-blind Phase 3 clinical trials in patients with active psoriatic arthritis (PsA). Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

The recommended dose for XELJANZ XR is 11 mg once daily. A dosage of XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not recommended for the treatment of PsA.

Study PsA-I (NCT01877668) had a duration of 12 months and enrolled patients who had an inadequate response to a nonbiologic DMARD and who were naïve to treatment with a TNF blocker. Study PsA-I included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months.

Study PsA-II (NCT01882439) had a duration of 6 months and enrolled patients who had an inadequate response to at least one approved TNF blocker. This clinical trial included a 3-month placebo-controlled period.

In these combined Phase 3 clinical trials, 238 patients were randomized and treated with XELJANZ 5 mg twice daily and 236 patients were randomized and treated with XELJANZ 10 mg twice daily. All patients in the clinical trials were required to receive treatment with a stable dose of a nonbiologic DMARD [the majority (79%) received methotrexate]. The study population randomized and treated with XELJANZ (474 patients) included 45 (9.5%) patients aged 65 years or older and 66 (13.9%) patients with diabetes at baseline.

During the 2 PsA controlled clinical trials, there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus non-biologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus non-biologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus non-biologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic arthritis patients treated with XELJANZ.

The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in rheumatoid arthritis patients.

Ankylosing Spondylitis XELJANZ 5 mg twice daily was studied in patients with active ankylosing spondylitis (AS) in a confirmatory double blind placebo-controlled Phase 3 clinical trial (Study AS-I) and in a dose ranging Phase 2 clinical trial (Study AS-II).

Study AS-I (NCT03502616) had a duration of 48 weeks and enrolled patients who had an inadequate response to at least 2 NSAIDs. Study AS I included a 16-week double-blind period in which patients received XELJANZ 5 mg or placebo twice daily and a 32-week open-label treatment period in which all patients received XELJANZ 5 mg twice daily.

Study AS-II (NCT01786668) had a duration of 16 weeks and enrolled patients who had an inadequate response to at least 2 NSAIDs. This clinical trial included a 12-week treatment period in which patients received either XELJANZ 2 mg, 5 mg, 10 mg, or placebo twice daily.

In the combined Phase 2 and Phase 3 clinical trials, a total of 420 patients were treated with either XELJANZ 2 mg, 5 mg, or 10 mg twice daily. Of these, 316 patients were treated with XELJANZ 5 mg twice daily for up to 48 weeks. In the combined double-blind period, 185 patients were randomized to and treated with XELJANZ 5 mg twice daily and 187 to placebo for up to 16 weeks. Concomitant treatment with stable doses of nonbiologic DMARDs, NSAIDs, or corticosteroids (≤10 mg/day) was permitted. The study population randomized and treated with XELJANZ included 13 (3.1%) patients aged 65 years or older and 18 (4.3%) patients with diabetes at baseline.

The safety profile observed in patients with AS treated with XELJANZ was consistent with the safety profile observed in RA and PsA patients.

Ulcerative Colitis XELJANZ has been studied in patients with moderately to severely active UC in 4 randomized, double-blind, placebo-controlled trials (UC-I, UC-II, UC-III, and dose-ranging UC-V) and an open-label long-term extension study (UC-IV).

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Induction Trials (Study UC-I, UC-II, and UC-V):

Common adverse reactions reported in ≥2% of patients treated with XELJANZ 10 mg twice daily and ≥1% greater than that reported in patients receiving placebo in the 3 induction trials were: headache, nasopharyngitis, elevated cholesterol levels, acne, increased blood creatine phosphokinase, and pyrexia.

Maintenance Trial (Study UC-III)

Common adverse reactions reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported in patients receiving placebo are shown in the following table.

Common Adverse Reactions* in -UC Patients during the Maintenance Trial (Study UC-III)

Preferred Term	XELJANZ 5 mg Twice Daily N = 198 (%)	XELJANZ 10 mg Twice Daily N = 196 (%)	Placebo N = 198 (%)
Nasopharyngitis	10	14	6
Elevated cholesterol levels**	5	9	1
Headache	9	3	6
Upper respiratory tract infection	7	6	4
Increased blood creatine phosphokinase	3	7	2
Rash	3	6	4
Diarrhea	2	5	3
Herpes zoster	1	5	1
Gastroenteritis	3	4	3
Anemia	4	2	2
Nausea	1	4	3

* reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported for placebo.

** includes hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

Dose-dependent adverse reactions seen in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections, serious infections, and NMSC.

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in XELJANZ-treated patients.

In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed in patients treated with XELJANZ 5 mg and 10 mg twice daily. Five cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer.

Polyarticular Course Juvenile Idiopathic Arthritis

XELJANZ/XELJANZ Oral Solution 5 mg twice daily or weight-based equivalent twice daily was studied in 225 patients from 2 years to 17 years of age in Study pcJIA-I and one open-label extension study. The total patient exposure (defined as patients who received at least one dose of XELJANZ/XELJANZ Oral Solution) was 351 patient-years.

In general, the types of adverse drug reactions in patients with pcJIA were consistent with those seen in adult RA patients.

Postmarketing Experience The following adverse reactions have been identified during post-approval use of XELJANZ/XELJANZ XR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Drug hypersensitivity (events such as angioedema and urticaria have been observed).

DRUG INTERACTIONS

The table below includes drugs with clinically important drug interactions when administered concomitantly with XELJANZ and instructions for preventing or managing them.

Clinically Relevant Interactions Affecting XELJANZ When Coadministered with Other Drugs

Strong CYP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ is recommended
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to tofacitinib and may result in loss of or reduced clinical response
Intervention	Coadministration with XELJANZ is not recommended
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Clinical Impact	Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, UC, or pcJIA.
Intervention	Coadministration with XELJANZ is not recommended

USE IN SPECIFIC POPULATIONS

All information provided in this section is applicable to XELJANZ as all contain the same active ingredient (tofacitinib).

Pregnancy

Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to XELJANZ during pregnancy. Patients should be encouraged to enroll in the XELJANZ pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call the toll free number 1-877-311-8972.

Risk Summary Available data with XELJANZ use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy. In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively. Further, in a peri- and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the recommended dose of 5 mg twice daily and approximately 36 times the maximum recommended dose of 10 mg twice daily, respectively.

The estimated 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. The background risks in the U.S. general population of major birth defects and miscarriages are 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

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 a rat embryofetal developmental study, in which pregnant rats received tofacitinib during organogenesis, tofacitinib was teratogenic at exposure levels approximately 146 times the recommended dose of 5 mg twice daily, and approximately 73 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the recommended dose of 5 mg twice daily, and approximately 29 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily, and approximately 6.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg twice daily, and approximately 1.5 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats that received tofacitinib from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily, and approximately 36 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats).

Lactation

Risk Summary There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in patients treated with XELJANZ, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of XELJANZ/XELJANZ Oral Solution or 36 hours after the last dose of XELJANZ XR (approximately 6 elimination half-lives).

Data Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured.

Females and Males of Reproductive Potential

Contraception *Females* In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility *Females* Based on findings in rats, treatment with XELJANZ may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible.

Pediatric Use

The safety and effectiveness of XELJANZ/XELJANZ Oral Solution for the treatment of active pcJIA have been established in patients 2 years to 17 years of age. Use of XELJANZ/XELJANZ Oral Solution for the treatment of pediatric patients with active pcJIA in this age group is supported by evidence from adequate and well-controlled studies of XELJANZ in adult RA patients with additional data from a clinical trial of XELJANZ/XELJANZ Oral Solution in pediatric patients (2 years to 17 years of age) with active pcJIA consisting of an 18-week, open label, run-in period followed by a 26-week placebo-controlled, randomized withdrawal period. The safety and effectiveness of XELJANZ/XELJANZ Oral Solution have not been established in pcJIA patients less than 2 years of age.

Adverse reactions observed in pediatric patients receiving XELJANZ/XELJANZ Oral Solution were consistent with those reported in RA patients.

Safety and efficacy of XELJANZ/XELJANZ Oral Solution in pediatric patients for indications other than pcJIA have not been established.

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

Geriatric Use

Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65.

Of the 1156 XELJANZ-treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients.

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Use in Diabetics

As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes.

Renal Impairment

Moderate and Severe Impairment

XELJANZ-treated patients with moderate or severe renal impairment had greater tofacitinib blood concentrations than XELJANZ-treated patients with normal renal function. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis).

Mild impairment

No dosage adjustment is required in patients with mild renal impairment.

Hepatic Impairment

Severe Impairment

XELJANZ has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ in patients with severe hepatic impairment is not recommended.

Moderate Impairment

XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib blood concentration than XELJANZ-treated patients with normal hepatic function. Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate hepatic impairment.

Mild Impairment

No dosage adjustment of XELJANZ is required in patients with mild hepatic impairment.

Hepatitis B or C Serology

The safety and efficacy of XELJANZ have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

OVERDOSAGE

There is no specific antidote for overdose with XELJANZ. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.

In a study in subjects with end stage renal disease (ESRD) undergoing hemodialysis, plasma tofacitinib concentrations declined more rapidly during the period of hemodialysis and dialyzer efficiency, calculated as dialyzer clearance/blood flow entering the dialyzer, was high [mean (SD) = 0.73 (0.15)]. However, due to the significant non-renal clearance of tofacitinib, the fraction of total elimination occurring by hemodialysis was small, and thus limits the value of hemodialysis for treatment of overdose with XELJANZ.

This brief summary is based on XELJANZ® (tofacitinib) Prescribing Information LAB-0445-23.0 Issued: December 2021

See XELJANZ full Prescribing Information at XELJANZPI.com

BANGALORE HOUSE CALL

On a highway traversed by cement trucks and Beetle-Bug auto-rickshaws we travel north from Bangalore, India, for a house call. It is 2007, and the city leaves us grudgingly. Between fields of loose chocolate soil and sprigs of beans poking skyward, the skeletons of homes and businesses rise; armies of workers lay brick from wooden scaffolds; hawkers sell car tires, shock absorbers, beds and tombstones.

Stanley Macaden, MD, an internist at Bangalore Baptist Hospital, inches our van forward in heavy traffic. In the back seat, two community health nurses chat quietly while Dr. Macaden reviews the details of our house call with me: "Thirty-one years old. Rheumatoid arthritis for 20 years. Non-ambulatory. It's a difficult case. She has much pain and often cries throughout our visit. She's cared for by her mother, who does a good job, but they are set in their ways. We'll take a look."

With each passing mile, the traffic thins and the rural nature of India declares itself. An egret stalks fish in a verdant pool of duckweed and water lilies. Hawks soar lazily overhead. Stands of palm trees shade thatch-roof homes. Wandering cattle, oblivious to traffic, stray into our lane and stop momentarily, chewing, flicking their tails. We turn off the paved road and bounce along a rolling dirt lane before pulling over at a low-set, tin-roofed hut facing a narrow alley. The dust settles as we gather our supplies. At the entry, cow dung has been dried into a hard, odorless welcome mat.

The Patient

Inside, I make out a rumpled sheet on a thin gray mat. It is rectangular, about three and a half feet long. Embers from the morning fire glow in the far corner of the hut. Light from the open entry sends a shaft of light to the edge of the sheet, and as my eyes adjust, I can make out a faint blue discoloration to the fabric. I lightly touch the smooth, velvety linen. The sheet rises and falls. Beneath my hand, there is a young woman.

Maria's mother squats next to the hidden form and coos a greeting as she unwraps the edge of fabric where a tuft of hair protrudes. A woman's head emerges. Her facial skin is like a newborn's: plump and fat, unwrinkled, downy hair around the lip and chin like the fuzz on a peach. Mother's and daughter's eyes meet. Another day begins.

Dr. Macaden squats down for a closer look, and I sit awkwardly, shifting unwilling knees in search of a comfortable position. The two nurses speak softly to Maria and her mother in the region's lilting Kannada tongue. "Our drive was pleasant. The fields look healthy. This is Dr. Macaden, whom you know. This is the American doctor. He is a specialist in arthritis and wants to help you."

The mother considers this as she runs a comb through her daughter's hair, humming softly. Then she reaches back into the shadows and hands a plastic bag to the nurses. One nurse empties the contents onto the mat, separates the pills into small piles, counts them and asks about effectiveness and side effects, while the other tallies the results in a notebook.

The older nurse asks, "Mother, do you give Maria this pill only once each week?" The mother nods solemnly. She explains that the mailman comes to the village once each week, and it is on this day she gives the special pill to Maria with a glass of water.

I recognize the methotrexate, diclofenac, cimetidine and a 10 mg tablet of prednisone and point to an unknown pill. Dr. Macaden whispers to me, "The pink pill is for depression."

Then, "Mother, do you give Maria the pink pill? Does she cry less?"

"Yes, I give her the special pill. Can you make it stronger? She still cries, but not all day."

"And how is her pain," Dr. Macaden asks.

"The pain is very bad," the mother says.

"Maria," Dr. Macaden places his hand lightly on her forehead. "How is your pain? Does the medication help with pain?" In a faint, hoarse whisper, Maria answers, "No. The pain is always with me, even when I sleep. I dream about the pain."

Dr. Macaden explains to me in English, "She is on morphine. It's a low dose, but it's not helping. She says the pain is no different. Perhaps you can take a look."

My Examination

A nurse asks Maria if I can examine her hands. I move closer, and she groans as I cradle her hand in my palm. The fingers overlap and droop in partial flexion, drifting uselessly away from the thumb. She cannot extend her fingers or pinch between her thumb and index finger. It's clear that she is unable to hold a glass or use a spoon. Her elbows are in a fully flexed state, the shoulders nearly immobile. Maria holds her arms crossed over her chest like a living sarcophagus. When I attempt to straighten her elbows or range her shoulders, there is an audible clunk, and she cries out and begins to sob.

Uncovering her lower legs, I understand why she cannot walk. The knees and hips are also contracted, her thighs nearly touching her abdomen, her knees flexed at 90º. If she were upright, she would appear in a perpetual squat. I rock her hip gently, and she cries out. There is roughly half a cup of fluid in each knee. Everywhere I lightly touch a joint, there is warmth and a hint of redness.

In such cases, something can always be done to help, to offer some measure of comfort, but I know my tools are limited. Hip, knee and shoulder replacement might restore her ability to walk and reduce pain, but finding an orthopedic surgeon willing to tackle the job—gratis, in an 80 lb. patient is a tall order. I make a mental note to ask Dr. Macaden on our way home if this is even a remote possibility.

"The methotrexate," I ask, "what is the dose?"

"Fifteen mg weekly," Dr. Macaden answers. "We wish we could increase the dose, but her liver enzymes are slightly elevated. We are giving her daily folic acid and will be drawing blood today."

I quietly evaluate our options. According to Dr. Macaden, hydroxychloroquine was discontinued years before due to a lack of efficacy. In the face of elevated liver enzymes, leflunomide is contraindicated.

"Sulfasalazine?" I ask. "Has she had a trial of sulfasalazine?"

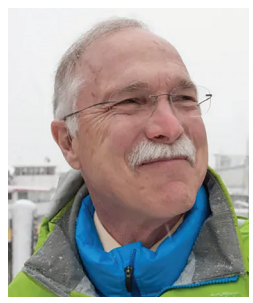
"To substitute for the methotrexate?"

"No, to add to it. It may be of some

continued on page 60

A patient's story

BY CHARLES RADIS, DO

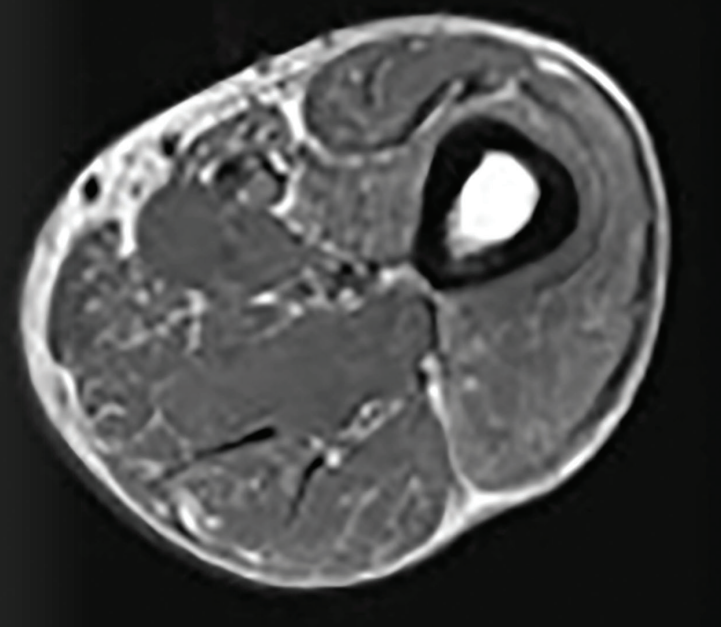


DR. RADIS

'We provide charity care at our hospital, but there are limits. For the cost of one year of Enbrel, we can provide immunizations to a thousand children.'

RADIOKAFKA / SHUTTERSTOCK.COM

THOUSAND-WORD PICTURES



A primer on imaging in myositis

■ BY ROCHELLE CASTILLO, MD, MS, ANDRO LICAROS, MD, & JEMIMA ALBAYDA, MD

DR. CASTILLO

DR. LICAROS

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In medicine, as in advertising, pictures can be worth a thousand words. From arthritis to vasculitis, imaging studies have been variably employed to aid in the diagnosis, treatment, risk stratification and prognostication of patients with rheumatic and musculoskeletal disorders. The same holds true with the idiopathic inflammatory myopathies (IIM), in which the clinical utility is high, despite the absence of imaging as a diagnostic variable in the latest European League Against Rheumatism (EULAR)/ACR classification criteria.[1]

These criteria—intended for research classification purposes and not diagnosis—took into account the availability of specific tests, and magnetic resonance imaging (MRI), the gold standard imaging modality for muscle, is not available in all regions. Nevertheless, imaging remains of particular importance in IIM because it provides an assessment of structural abnormalities in muscle tissue, which can help confirm the presence of disease, delineate the type and pattern of its involvement and, ultimately, help guide treatment.

MRI: Myositis Routine Imaging?

MRI provides excellent soft tissue resolution and contrast, allowing for the evaluation of the extent and distribution of edema, fatty/fibrous replacement and atrophy, and is the main workhorse when it comes to muscle imaging. It is useful for diagnostic purposes to confirm muscle involvement in a patient with suspected disease and can pinpoint potentially high-yield sites for muscle biopsy, albeit not in real time. In some instances, it can help differentiate among the IIM subgroups based on muscles involved and distinguish them from common mimics (see Table 1, below).

The MRI myositis protocol involves T1-weighted imaging (T1W) and fluid-sensitive T2W with fat suppression *or* short-tau inversion recovery (STIR) sequence in the axial and coronal planes.[2,3] Gadolinium contrast is not required unless fasciitis, focal myositis or a cystic or solid mass lesion are of primary concern.[4] In IIM-affected muscle, T2W and STIR hyperintensities depict edema and increased water content characteristic of active muscle inflammation or necrosis in the acute phase (see Figure 1B, opposite). T1W hyperintensities delineate fatty replacement which is a marker of damage and chronicity (see Figure 1A, opposite). Calcinosis can be detected on all sequences as signal voids (see Table 1, below).

A whole-body MRI would be ideal in that it can yield precise patterns of preferential muscle involvement or sparing, making it possible to detect disease-specific muscle signatures or fingerprints. Clinically, however, it is time consuming and cost inefficient. Thus, an MRI of the thigh or of the upper extremity is typically employed, and generally sufficient, for the evaluation of IIMs. In the same vein, while higher magnetic strengths may yield crisper images, the 1.5 Tesla (1.5T) MRI does not appear to fare worse than the 3.0T for the purposes of MSK imaging.[5]

Even after the diagnosis of IIM has been established, MRI remains useful to monitor response to treatment, qualitatively measure disease activity, and direct future management. This is particularly important when discordance exists between the patients' symptoms and providers' assessments and when routine serologic markers of muscle breakdown fail to correlate with clinical findings. Active disease requiring escalation or modification of therapy is indicated by more pronounced muscle edema, whereas response to therapy appears as resolution or reduction of edema (normalization of intensity values or "return to isointensity" in the above sequences). Notably, a relationship between the degree of STIR hyperintensity and the abundance of pre-treatment inflammatory infiltrates on muscle biopsy has been shown in several studies.[4,6]

On the other hand, intensification of the largely irreversible markers of chronicity and damage, such as fatty replacement and atrophy (increased signal intensity and decreased muscle mass, respectively, on T1W), warrant reevaluation of the drug regimen to balance out the need to prevent both disease progression and unnecessary exposure to potentially harmful medications. Quantitative MRI studies have similarly demonstrated a modest correlation between the extent of fatty infiltration noted on MRI and that seen on muscle histopathology.[7,8]

Thus, the capacity of MRI findings to correlate with response to therapy underscores its value in guiding subsequent decision making. With its versatility, granularity and increasing ubiquity, it's easy to see why MRI is the go-to muscle imaging modality (see Table 2, p. 60).

Ultrasound

Ultrasound is undeniable proof that oldies can still be goodies. With the advent of higher frequency probes, imaging resolution for soft tissue is now far higher than MRI and offers a close-up view of the muscle, which has its own advantages. Ultrasound also has more widespread availability, portability, cost efficiency, and real-time imaging capability, with the latter rendering it a useful tool for optimizing muscle biopsy site selection as well as for detecting abnormal muscle movements (see Table 2, p. 60). However, ultrasound is heavily operator dependent, and knowledge of both proper image acquisition and image interpretation for muscle is needed.

On ultrasound, normal muscle is relatively anechoic (black) or hypoechoic (gray) and interspersed with hyperechoic (white) perimysial septa, which gives it a starry sky

TABLE 1: FEATURES OF IIMs ON MRI

DIAGNOSIS	MRI
Dermatomyositis and polymyositis	• Edema: hyperintensity +/- increase in muscle volume (T2W and STIR), can be diffuse or focal • Fatty infiltration: focal or diffuse hyperintensity in muscles (T1W) • Atrophy: decrease in muscle volume (T1W) • Fasciitis: focal or symmetric hyperintensity (T2W, STIR, contrast enhanced) with thickening of superficial fascia or septa • Calcinosis: low signal intensity foci in soft tissue (all sequences)
Inclusion body myositis	• Prominent fatty-fibrous infiltration and atrophy of distal quadriceps muscles with relative sparing of the rectus femoris; more involvement in the anterior rather than posterior compartment of the thigh • "Undulating fascia sign"—wavy fascia between the atrophic and fat-infiltrated vastus intermedius and vastus lateralis muscles
Immune-mediated necrotizing myopathy	• More pronounced edema, early fatty replacement and atrophy compared with other subtypes

AJT / SHUTTERSTOCK.COM

appearance on cross-section (see Figure 1E, right). Longitudinally, the parallel orientation of muscle fibers is appreciated. Myopathic muscle is marked by an increase in muscle echointensity, mild in acute muscle edema, with a more marked increase with fatty fibrous replacement. Changes in muscle architecture are also seen, as well as loss of visualization of structures deeper to the muscle (attenuation) when pathology is severe (see Figure 1D, right).

In cases of acute edema, a *see-through echogenicity* is described, in which there is no attenuation of ultrasound waves despite an increase in muscle echointensity.[9] Notably, acute myopathic changes can be subtle, and detecting edema may be inconsistent on ultrasound. Ultrasound is very useful, however, to pick up chronic changes given its sensitivity for fat, fibrosis and atrophy. Unlike MRI where different sequences can delineate either edema or fatty replacement, ultrasound shows a combination of all pathology in one B mode image. In terms of vascularity, a few studies suggest that higher Doppler scores are seen with acute myositis.[10,11] Although the use of Power Doppler is a must in inflamed joints, a need exists for better standardization for muscle because perfusion is affected by multiple factors, including activity and muscle contraction.

Ultrasound has been gaining traction for diagnostic purposes especially in chronic myositis, such as inclusion body myositis (IBM) in which the specificity of the affected muscles can help distinguish it from mimics.[12] It may find more use as a follow-up tool in treatable cases of myositis by showing the successful resolution of increased muscle echogenicity or the development of fatty, fibrous replacement. The routine use of such modalities as elastography, evaluating tissue stiffness, may provide further information about muscle quality in the future. Despite the formidability of MRI for myositis, ultrasound is a viable alternative in the hands of experienced operators.

PET

On the other end of the innovation spectrum is metabolic imaging—the nuclear imaging technique of positron emission tomography (PET), which is most often combined with computed tomography (CT) or MRI to provide concurrent metabolic and anatomic information of tissues. The most commonly used tracer of ^{18}F-FDG picks up an increase in glycolysis that occurs in the setting of inflammation.

Other tracers—such as ^{15}O-water, which detects blood flow, and ^{11}C-L-methyl-methionine, which targets amino acid transport—have been used to evaluate skeletal muscle; however, their considerably shorter half-lives compared with ^{18}F-FDG translate to shorter—and thus less optimal—post-injection imaging windows.[13,14] For IBM specifically, the amyloid markers ^{11}C-PIB[97] and ^{18}F-florbetapir and the *tau* marker ^{18}F-THK5317 may have value in differentiating IBM from other IIMs.[15-17]

It is important to note that not all instances of MRI-detected muscle edema in IIM correlate with an increase in ^{18}F-FDG activity. The detection of increased ^{18}F-FDG activity may provide another layer of information regarding the disease process (see Figure 1C, right). Additionally, its utility in screening for malignancy in newly diagnosed or refractory cases of myositis is being invoked, as well as its ability to follow interstitial lung disease.[18,19]

PET imaging may be uniquely advantageous to the subset of patients considered at high risk for malignancy and interstitial lung disease based on autoantibody status and other predictors (see Table 2, p. 60). PET/MR, which offers higher soft tissue contrast than PET/CT without the ionizing radiation, may yet emerge as a mainstream modality in IIM imaging.

Conclusion

A thorough clinical evaluation aided by serologic and histopathologic findings remain at the forefront of the assessment and management of IIMs; however, there is plenty of room to harness the power of imaging studies, such MRI, ultrasound and multimodal PET to better characterize disease parameters across the entire clinical trajectory. While each modality can certainly hold its own in the myositis imaging space, they can also be used either simultaneously or sequentially to paint the most accurate picture of a patient's condition over time.

Capitalizing on the major strengths of each imaging approach—the clarity for muscle edema vs. fat/fibrosis with MRI, the real-time and dynamic assessment with ultrasound, and the physiologic information of PET—can provide clinicians with the images that best capture what is needed to positively influence decision making and overall outcomes.

With the broad shift toward less invasive, more patient-centric approaches in all aspects of patient care, these pictures will certainly be worth far more than a thousand words in the not-too-distant future. **R**

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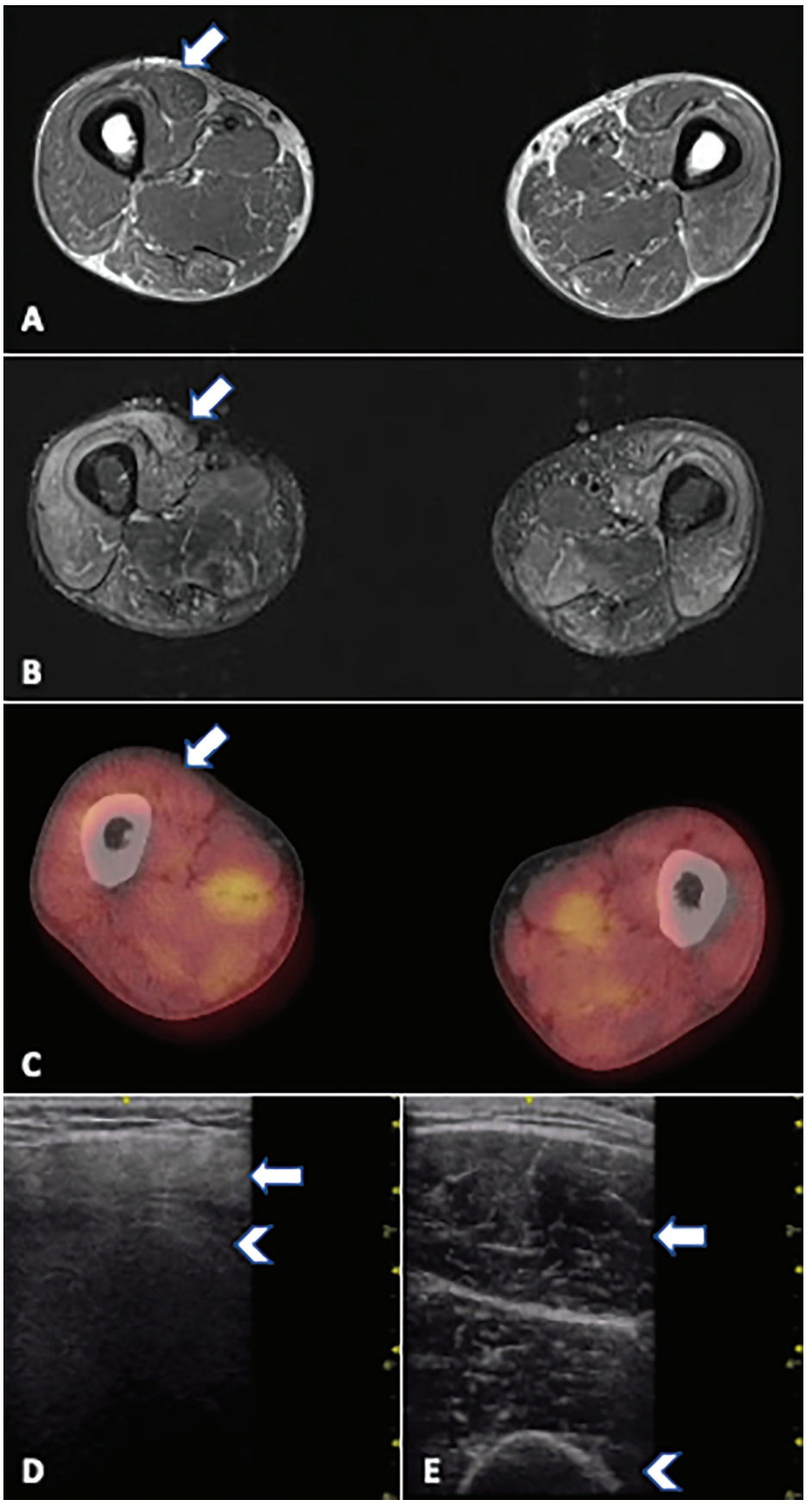
FIGURES 1A–1E



MRI, PET/CT and ultrasound in a 33-year-old man with refractory PM-Scl dermatomyositis. Arrows: rectus femoris; arrowheads: humerus.

A) MRI of the thighs (T1W) showing no significant fatty replacement. B) MRI of thighs (STIR) with mild to moderate muscle edema (increased signal) mainly in anterior compartment. C) PET/CT showing symmetric bilateral increased FDG uptake in scattered muscles, especially pelvic adductors, D) increased muscle echointensity in the rectus femoris with attenuation (loss of bone echo of underlying femur) and atrophy in comparison with E) normal rectus femoris in age-matched control.

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continued on page 60

Thousand-Word Pictures *continued from page 59*

TABLE 2: COMPARISON OF STRENGTHS & WEAKNESSES OF MRI, ULTRASOUND & PET/CT

	MRI	ULTRASOUND	PET
Strengths	• Excellent soft tissue resolution and contrast • Identifies potential biopsy sites • Scans large areas of muscle at a time • Better at evaluating deeper structures • Can help differentiate among major subgroups based on regional patterns	• Easily available • Non-ionizing, no contraindications • Can be done at bedside • Real time imaging, permits dynamic muscle testing • Identifies potential biopsy sites • Can differentiate among major subgroups based on preferential pattern of muscle involvement • Less expensive	• Provides functional information • Concomitantly screens for malignancy and evaluates ILD • Identifies potential biopsy sites • Scans large areas of muscle and other organs
Weaknesses	• Time consuming (40-50 minutes) • Less easily accessible and more expensive • Contraindicated in certain patient groups (metal implants, pacemakers) • Can be claustrophobic	• Limited visualization of deep musculature • Covers relatively small area of muscle at a time • US can underestimate edema • More susceptible to operator dependence/expertise at both the scanning and interpreting stages • Quality and sensitivity vary with body habitus • Not fully standardized	• Radiation exposure (with CT) • More expensive than US and MRI • Not fully standardized • May be less accessible than US or MRI

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Bangalore House Call *continued from page 57*

benefit," I answer. Dr. Macaden jots down the dosage and silently nods. "And the prednisone, perhaps you can nudge that up as well," I add.

Foremost in my mind is whether a trial of a biologic could be prescribed, but before I could ask, Dr. Macaden says, "Enbrel was suggested last year, but it's not available for her. We provide charity care at our hospital, but there are limits. For the cost of one year of Enbrel, we can provide immunizations to a thousand children." He was silent for a moment. "There are many Marias."

I draw up four cortisone injections for Maria's knees and shoulders, identifying them as the most symptomatic joints. Maria's mother softly explains to her daughter that the needle will hurt, but the shots will help with pain. I have been told by my Indian co-workers that injections are held in high esteem by the local population. It is what separates traditional healers from physicians—and a sign that a doctor is doing all they can to improve their patient's illness. I scrub the injection sites thoroughly, acutely aware that I am injecting the knees and shoulders of a woman who is non-ambulatory and spends her days underfoot in the loving care of her mother and siblings. The injections will help … for a few weeks, a month or two at most, but long-term, meaningful improvement will only come with a combination of joint replacement and the addition of a biologic.

It is a difficult truth, but at 31 years of age, Maria is slowly, inexorably dying.

Reflections

On the way back to the city, I reflect on Maria. Although it is 2007, I feel like I have been transported back to my first year in practice in 1985, to the many failures of treatment our patients suffered through. Older rheumatologists can still remember when we relied on gold, capable of placing a few patients in remission, but fraught with side effects and ineffective for the majority. Methotrexate was utilized, but often cautiously, and in relatively low doses.

At my weekly rheumatology conference at Maine Medical Center, Phil Thompson MD, 20 years my senior, recalled hospitalizing patients with rheumatoid arthritis with complications of the disease we rarely see today: vasculitis, pleuro-pericardial effusions, secondary amyloidosis and infections from high-dose corticosteroid treatment. Despite his best efforts, these patients frequently died.

I remember my grandfather, Rice Beavers, afflicted for the last seven years of his life by a combination of rheumatoid arthritis and Parkinson's disease in rural West Virginia in the early 1970s. Once a vibrant blacksmith and farmer, year by year he was beaten down to a state of helplessness and dependency. A hired man lifted him from bed each day into his wheelchair, dressed him, bathed him and strapped a spoon to his hand so he could feed himself. Two years before he died, he was bedbound and no longer able to feed himself.

From time to time, I consult on *old-time* patients with rheumatoid arthritis in my practice in northeast Maine—patients whose disease has inexorably progressed without a trial of an aggressive disease-modifying anti-rheumatic drug or biologic.

Just four months ago, I received a phone call about a family fleeing the war in their native Ukraine with their 5-year-old daughter, who had previously been diagnosed with juvenile idiopathic arthritis. They arrived in Maine with nothing but the clothes they could carry. The girl was beginning to flare. I called Ed Fels, a pediatric rheumatologist, who cut through the red tape and promptly arranged for her to restart adalimumab. But what if they had landed in a refugee settlement? What if adalimumab were simply unavailable?

It is in these moments that I remember Maria, the burden of disease she carried and the loving care she received from her family and healthcare workers.

We should never take for granted the immense progress basic science, clinical trials and the availability of effective treatment has made in our patients' lives. There were once many Marias, but there are far fewer today, and for that we should be thankful. **R**

This essay was originally written in 2007, while Charles Radis, DO, was a visiting attending at Bangalore Baptist Hospital, India. Since then, Bangalore Baptist Hospital has grown considerably and now has a rheumatologist on staff. Dr. Radis continues to practice part time in Maine and is a clinical professor of medicine at the University of New England, College of Osteopathic Medicine. He can be reached at cradis@maine.rr.com or through his website at www.doctorchuckradis.com.

Clinician, Scientist, Historian

An interview with Dr. Eric Matteson

BY JASON LIEBOWITZ, MD

Rheumatologists who are outstanding clinicians, provide consistently exceptional care to patients and serve as role models for colleagues and trainees are in the spotlight in our Lessons from a Master Clinician series. Here, we offer insights from clinicians who have achieved a level of distinction in the field of rheumatology.

Eric L. Matteson, MD, MPH, is professor of medicine and chair emeritus of the Division of Rheumatology in the Department of Internal Medicine at the Mayo Clinic. Dr. Matteson's clinical and research interests are in the fields of vasculitis and inflammatory arthritis. His research agenda includes investigation into the epidemiology of these diseases and their clinical disease expression and impact on patients who have them, biomarkers of disease susceptibility and disease activity, and clinical trials of novel agents. This work has resulted in more than 350 publications.

Dr. Matteson has served on the steering committee of the international study consortium investigating lung disease in the connective tissue diseases and has served as co-principal investigator for clinical and translational studies of polymyalgia rheumatica.

He is a past president of the Rheumatology Research Foundation, and he has authored or co-authored six books about the history of rheumatic disease and rheumatologists (**https://tinyurl.com/5n99chtx**).

***The Rheumatologist (TR)*: In your opinion, what makes for a master clinician?**

ELM: This is something that is often asked, and there are many wonderful insights on this subject that ought to be shared. One response that I don't hear much is perhaps something that I trained in myself, and I know others who I regard as master clinicians have done the same: from the time of my undergraduate studies through medical school, I found it extremely important to have a structure for my reading program. This included daily pensum (in the positive sense) of reading and reviewing specific medical topics and, also, dedicated time for reading on a nonmedical topic. For me, the latter was usually something of a historical nature or a classic work of literature.

***TR:* Who were some of your clinician role models, and what qualities did you admire in these individuals?**

ELM: In my fellowship, William "Joe" McCune, MD, at the University of Michigan, Ann Arbor, was an important role model. Joe demonstrated the traits that I admire and that I sought to emulate: He was a great listener, thoughtful, considerate, very knowledgeable, energetic and sensitive, not only to the needs of patients, but also to those of learners. He was very tuned in to subtle discrimination and bias against women and minorities on our team, and he was effective in addressing it. That impressed me greatly and became important as I faced these same challenges in promoting the careers of our faculty. He had a great clinician's eye for clinical knowledge gaps and how to address them, and he really got me, and many others, started in our clinical academic careers.

As someone interested in medical history, I have also looked to physicians like William Osler and Adolf Kussmaul as figures who were outstanding clinicians. Lessons from them, like lessons from my own role models in training and thereafter, are the importance of performing self-critique, having a willingness to reevaluate a difficult problem time and again, being able to openly admit mistakes and act upon them in a positive way that ultimately enhances patient care, and working to achieve excellence in teaching.

***TR:* For a fellow in training or junior rheumatologist, what are some habits that can be incorporated into daily practice to build on their skills as a clinician?**

ELM: The question is a good one: I don't know of any magical way to build skills other than to practice them. There is no substitute for seeing patients, and it is important to not shy away from seeing patients in large numbers over time. Most of what I have learned in medicine, and a lot of what I have learned in life even outside medicine, has been the result of my interactions with patients. I've already mentioned the habit of reading daily.

All of this is hard work, and it simply must be done to reap the rewards. Medicine isn't an 8 to 5 job. It is a privilege and one that must be earned and deserves our hard work.

Another important feature of success is to develop a sound mentorship relationship—often more than one—and to work assiduously to develop a peer network for professional and personal support.

***TR:* What lessons have you learned from patients that have contributed to your own growth as a clinician?**

ELM: One of the most important things that I have learned is personal awareness and resilience. Many of our patients suffer from chronic, complex diseases. I have had powerful experiences in both success and also in failures of care that have made me more empathetic and shown me how important it is to listen, guide, and also honor the personal agency of not only patients, but also learners at different levels, as well as of colleagues and friends.

I'll never forget a young woman I met early in my career. She had a rare autoinflammatory disorder with recurrent macrophage activation syndrome. She had two small children, a husband deployed with the Army and wonderful patience. We figured out the diagnosis, and she initially, to our gratification, responded to treatment, but over a year-and-a-half she suffered multiple relapses and died. It was incredibly heart-breaking. Today, we might have been able to save her with some of our newer therapies. I feel that I got to know a wonderful person and family during her care and at her funeral. It was a real lesson about the importance of understanding disease and patients and humility.

***TR:* What skills, habits or experiences have you found most helpful in finding the right diagnosis in medical mystery cases that heretofore had been unsolved?**

ELM: These mystery cases are what really interest and even delight us in rheumatology, and these cases may serve as professional and personal satisfiers in terms of intellectual stimulation and ability to make an impact. As I mentioned, there is no substitute for seeing lots of patients and keeping up on reading in the field. Only in this way can you learn the breadth and subtleties of disease and recognize unusual symptom complexes that can characterize these conditions.

Constantly going back to the patient to understand signs and symptoms, consulting the literature and your peers, and seeking advice from others are essential to cracking these cases, and sometimes even recognizing new disease entities. It is very thrilling to recognize a disease in a patient who has been sent to you after seeing many physicians and not receiving a diagnosis, but I must also say that I have often been just as thrilled when someone on our team comes up with the correct diagnosis. Sometimes you recognize the disease right from the history and exam at the first encounter but, more often, the diagnosis comes with carefully working through the disease features over some time.

***TR:* How do you approach the concept of uncertainty when entertaining a diagnosis for a patient?**

ELM: If there is anything certain in medicine, it is uncertainty. Uncertainty is something that consciously, or sometimes unconsciously, should be taken into account by being as meticulous as possible in considering diagnostic possibilities and in developing treatment plans. It can have bad consequences in the form of over-diagnosis and over-treatment; in my experience; the latter is by far the most common and may lead to horrendous consequences. In our discipline of rheumatology, we become very humble by the variability of response to our treatments.

Uncertainty is inherent to the patient experience, too. For this reason, it is really important to focus on developing trust with patients and their families and to focus on shared decision making. R

DR. MATTESON

> There is no substitute for seeing lots of patients & keeping up on reading in the field.

Jason Liebowitz, MD, completed his fellowship in rheumatology at Johns Hopkins University, Baltimore, where he also earned his medical degree. He is currently in practice with Skylands Medical Group, N.J.

Difficult-to-Treat RA: New Hope?

New EULAR definition & management points to consider

BY SAMANTHA C. SHAPIRO, MD

Despite an expanding armamentarium of disease-modifying treatments for rheumatoid arthritis (RA), some patients with RA remain symptomatic.[1] Current treatment guidelines from both the ACR and the European Alliance of Associations for Rheumatology (EULAR) recommend treat-to-target strategies to achieve remission or low disease activity, and patients want to feel better.[2,3] So how can we best help patients with difficult-to-treat (D2T) RA?

In 2020, EULAR took the first steps toward evidence-based guidance for this population, publishing two articles that address the definition and management of difficult-to-treat RA. Here, lead author György Nagy, MD, PhD, DSc, head of the Department of Rheumatology and Clinical Immunology, and professor, Department of Genetics, Cell and Immunobiology, Semmelweis University, Budapest, Hungary, offers insights on what this work means for practicing rheumatology providers and our patients.

Difficult-to-Treat RA Defined

The first step in solving any problem is properly identifying it. By way of results from an international survey of rheumatologists and expert opinion, a multidisciplinary task force created the EULAR definition of D2T RA.[4] The task force defined the condition by three mandatory criteria (see Figure 1, below).

Simply stated, D2T RA can be summarized as a patient who has 1) failed two or more biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDS or tsDMARDs) with different mechanisms of action (MOA) after failing conventional synthetic DMARDs; 2) has active disease; and 3) has poorly controlled disease as perceived by the rheumatologist and/or patient.

If you're reading these criteria and thinking to yourself, "I could name 20 patients who meet these criteria without even trying," welcome to the club. An international survey of rheumatologists confirmed the unmet needs of this group.[5] These patients are more common than we'd like them to be, especially given the myriad therapeutic options now at our disposal.

Uniform terminology and a clear definition of D2T RA are the first steps toward designing clinical trials to better care for this population. Professor Nagy said, "The definition is necessary to select the appropriate patient population, and our EULAR definition was the first precise characterization of this important patient cohort."

This definition still needs to be validated, but the Nagy et al. hope the "definition presented here will provide a robust and consistent identification" of these patients, as well as a "platform to define a group of similar patients for research."

FIGURE 1: EULAR DEFINITION OF D2T RA[4]

1. Treatment according to EULAR recommendation and failure of ≥2 b/tsDMARDs (with different mechanisms of action)* after failing csDMARD therapy (unless contraindicated).†
2. Signs suggestive of active/progressive disease, defined as ≥1 of:
   a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR >3.2 or CDAI >10).
   b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other).
   c. Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent).
   d. Rapid radiographic progression (with or without signs of active disease).‡
   e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life.
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

All three criteria need to be present in D2T RA.

Key: b, biological; CDAI, clinical disease activity index; cs, conventional synthetic; DAS28-ESR, disease activity score assessing 28 joints using erythrocyte sedimentation rate; DMARD, disease-modifying anti-rheumatic drug; mg, milligram; RA, rheumatoid arthritis; ts, targeted synthetic.

*Unless restricted by access to treatment due to socioeconomic factors.

†If csDMARD treatment is contraindicated, failure of ≥2 b/tsDMARDs with different mechanisms of action is sufficient.

‡Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥5 points at 1 year.

Causes

True to autoimmune form, the cause of D2T RA is multifactorial. RA may pose a clinical challenge due to true resistance of disease to DMARDs, or limited drug options due to adverse effects and/or patient comorbidities. Treatment non-adherence is associated with higher disease activity levels, and may lead to inappropriate treatment switches and reduced quality of life.[6] And non-inflammatory symptom contributions from fibromyalgia, osteoarthritis, or psychosocial factors associated with poor coping also play a role.[7]

Management

With the problem defined, EULAR developed evidence-based points to consider (PtCs) for the management of D2T RA via systematic literature review and expert consensus (see Figure 2, opposite).[8]

First, the authors stress two overarching principles: 1) PtCs apply to patients who meet the EULAR definition for D2T RA (see Figure 1, left); and 2) the "presence or absence of inflammation should be established to guide pharmacological and non-pharmacological interventions." Specifically, "concomitant fibromyalgia, osteoarthritis, and/or psychological conditions, nonadherence, and comorbidities like infections and cancer may contribute to the D2T state" and thus need to be considered when a patient isn't responding the way we'd like.[9]

When it comes to differentiating inflammatory from noninflammatory disease activity, ultrasonography can be a useful adjunct to physical exam, but the evidence for biomarkers and other imaging modalities is less convincing.[10,11]

Next, the authors urge us to consider the possibility of misdiagnosis as a reason for nonresponse to therapy. That is to say, if the patient isn't getting better despite multiple different therapeutic interventions, take a step back and reconsider the underlying diagnosis. Many conditions, such as crystalline arthritis, vasculitis, cancer and chronic infections, may mimic RA. Professor Nagy shares, "I would say [misdiagnosis] is common in my clinical experience, especially if the patient has seronegative RA or RA that is not clinically typical."

Treatment adherence should be directly discussed and optimized via shared decision making. "[Assessing nonadherence] is a really essential and complex question. Questionnaires and surveys may help, and serum drug levels might be measured as well—although they generally aren't part of routine care," Professor Nagy says.

Another EULAR article provides specific guidance regarding assessment of nonadherence in rheumatic and musculoskeletal disorders.[12]

As to new bDMARD or tsDMARD selection after failure of two drugs with differing MOAs, the evidence currently doesn't identify a preferred drug class. The PtCs suggest switching to a drug with a new MOA at the maximum dose deemed effective and safe for the patient. "We need more trials to have evidence-based information regarding the best possible option in different clinical cases," Professor Nagy says.

Lastly, the PtCs encourage the use of non-pharmacological modalities like exercise,

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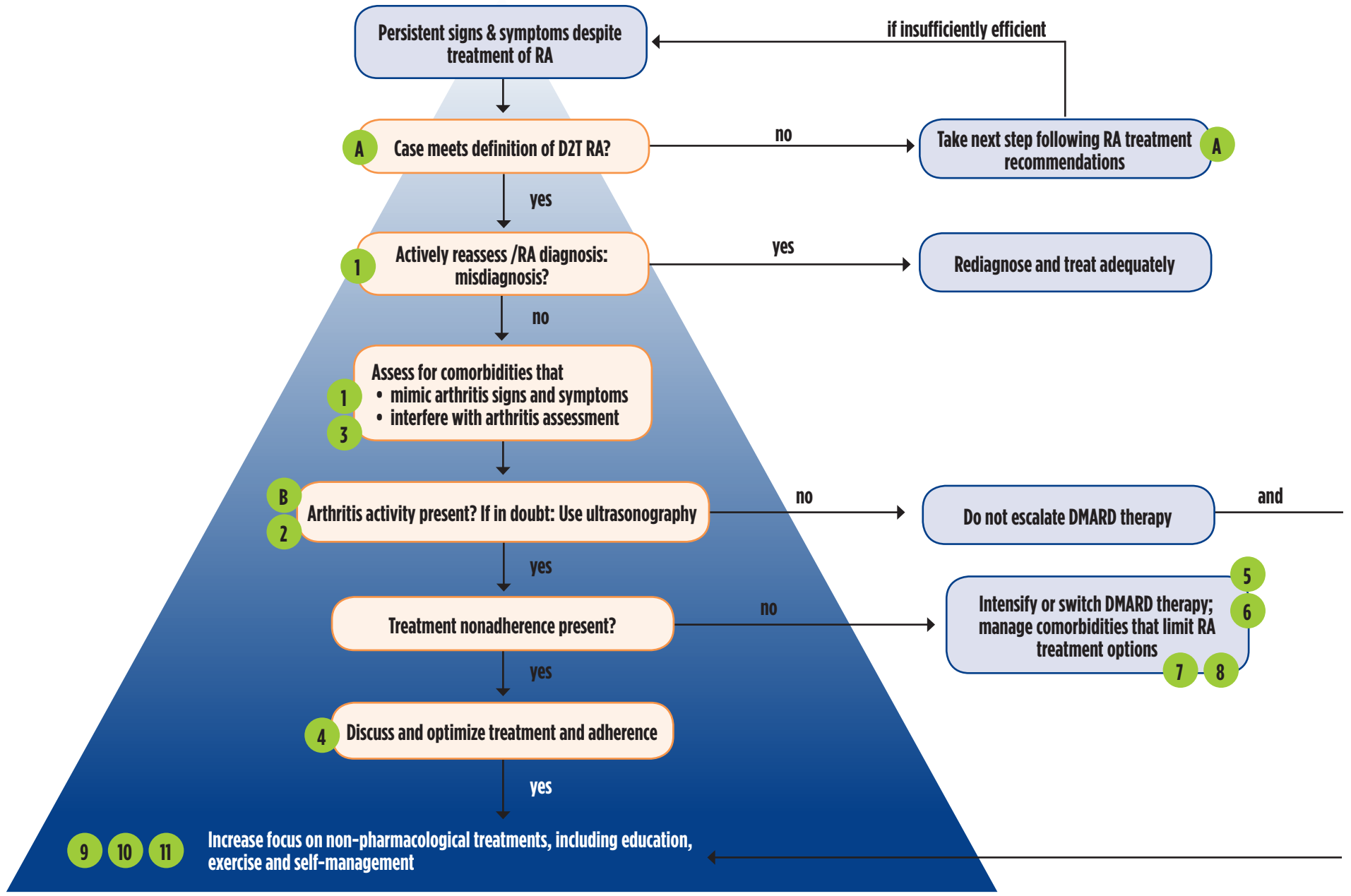
FIGURE 2: ALGORITHM BASED ON THE EULAR PTCS FOR THE MANAGEMENT OF D2T RA[8]



The pyramid background with increasing intensity of blue color indicates non-pharmacological approaches and treatments, which are important throughout all phases of RA, but especially so if pharmacological treatment options are limited. The letters and numbers indicate the corresponding overarching principles and PtCs, respectively.

Key: **D2T, difficult-to-treat; DMARD, disease-modifying anti-rheumatic drug; EULAR, European Alliance of Associations for Rheumatology; PtCs, points to consider; RA, rheumatoid arthritis.**

psychological interventions (e.g., cognitive behavioral therapy) and education in all patients with D2T RA.[13] Increasing self-efficacy—the ability to control or manage various aspects of their disease—profoundly impacts the well-being of patients.[14]

Professor Nagy says, "Non-pharmacological therapy, self-management programs and exercise are essential in RA. Clearly, more well-designed trials are needed [in this regard] too."

High-quality evidence to guide recommendations was scarce, leading to low strength of recommendations. But the Task Force proposed an agenda to help guide further research. Professor Nagy states, "The definition is new. D2T RA is a whole new entity. We hope that there will be significant interest regarding our work, and that our proposal will be used in daily clinical practice and promote further research."

Conclusion

EULAR has taken an important step forward in improving the care of our patients with D2T RA. A standardized definition may inform future clinical trials, and evidence-based guidance for the care of this population may lead to improved outcomes. Professor Nagy concludes, "This is the major message of our work: avoid overtreatment [and also overdiagnosis])!" R

Samantha C. Shapiro, MD, is an academic rheumatologist and an affiliate faculty member of the Dell Medical School at the University of Texas at Austin. She is a member of the ACR Insurance Subcommittee.

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taltz® (ixekizumab) injection 80 mg/mL

FOR PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS

Rapid ACR20 response seen as early as week 2 in some patients[1-3]

CITRATE-FREE

FDA Approved[4]

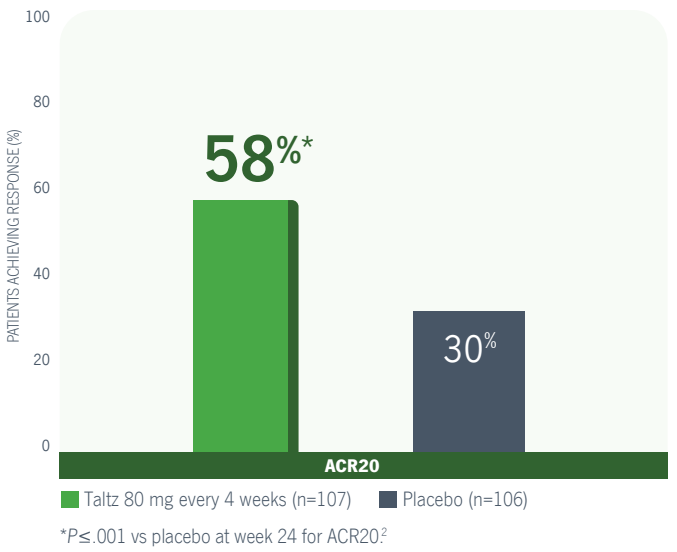
SPIRIT-P1 ACR20 AT WEEK 2: TALTZ 39% VS PLACEBO=13%

SPIRIT-P2 ACR20 AT WEEK 2: TALTZ 38% VS PLACEBO=12%

ACR20 at week 2 was not controlled for type 1 error; therefore, statistical conclusions cannot be made.

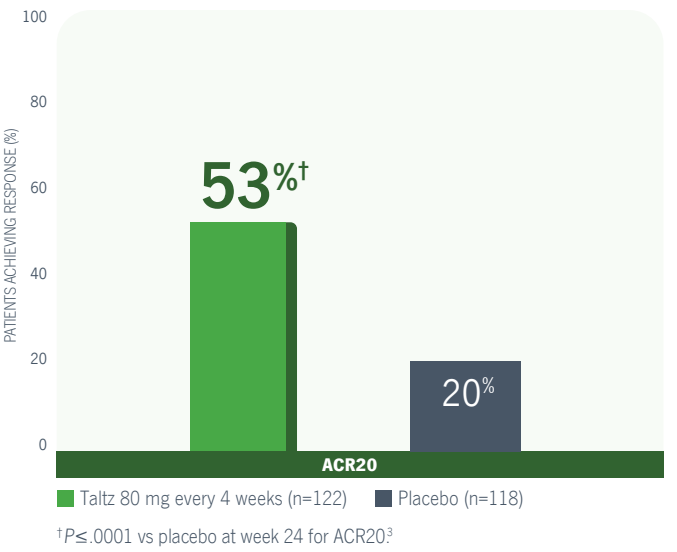
Consistent joint symptom results regardless of TNFi experience[2-4]

SPIRIT-P1 (BIOLOGIC-NAIVE): ACR response rates at week 24, NRI[2,4]



*$P \leq .001$ vs placebo at week 24 for ACR20.[2]

SPIRIT-P2 (TNFi-EXPERIENCED): ACR response rates at week 24, NRI[3,4]



†$P \leq .0001$ vs placebo at week 24 for ACR20.[3]

NRI of intent-to-treat population through week 24.

Inadequate responders (<20% improvement in tender and in swollen joint counts) at week 16 were analyzed as nonresponders after week 16 until the primary endpoint[1]

Primary endpoint=ACR20 response at week 24.

SPIRIT-P1 and -P2 Trial Design[3-6]

SPIRIT-P1 (N=417) and -P2 (N=363) were phase 3, randomized, double-blind, placebo-controlled trials to evaluate the efficacy and safety of Taltz compared with placebo in patients with active psoriatic arthritis. Patients in SPIRIT-P1 were biologic-naive. Patients in SPIRIT-P2 were tumor necrosis factor inhibitor (TNFi)- experienced, having had an inadequate response and/or intolerance to 1 or 2 prior TNFis. In both trials, the primary efficacy endpoint was the proportion of patients achieving ACR20 response at week 24. All patients were ≥18 years of age and had ≥3 swollen and ≥3 tender joints. Patients were randomized to placebo or Taltz 80 mg every 2 or 4 weeks following a 160 mg starting dose. In SPIRIT-P1, an active reference arm of adalimumab 40 mg every 2 weeks was included. Patients in all study arms were allowed to continue taking stable background medications during the trial. Inadequate responders (as defined by blinded criteria of <20% improvement in tender and in swollen joint counts) at week 16 received rescue therapy and were analyzed as nonresponders after week 16 until the primary endpoint. After receiving rescue therapy, inadequate responders in the placebo and adalimumab arms were re-randomized to Taltz 80 mg every 2 or 4 weeks. NRI methods were used for categorical efficacy analyses during the double-blind treatment period.

ACR=American College of Radiology; TNFi=tumor necrosis factor inhibitor; NRI=nonresponder imputation.

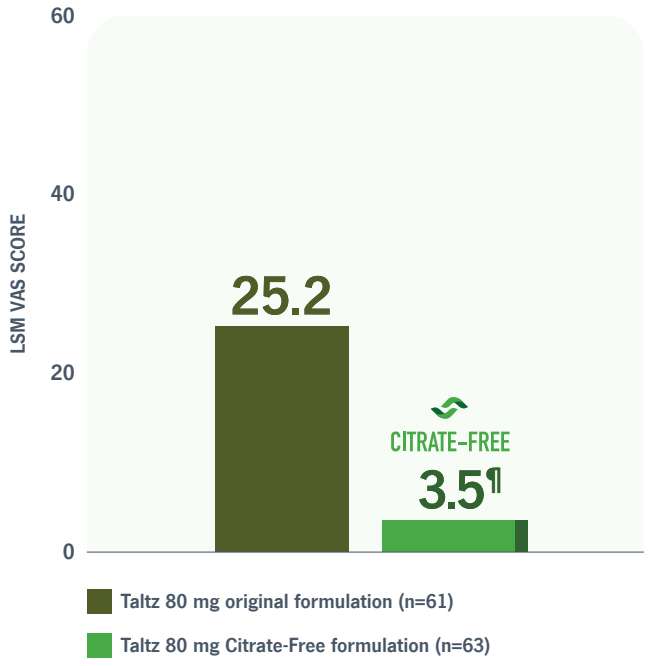
Please see Important Safety Information on adjacent page.

Please see Brief Summary of Prescribing Information on the following pages. Please see Instructions for Use included with the device.

Taltz is FDA approved in a citrate-free formulation[4]

Same Taltz,‡ less injection site pain§

VAS Injection Site Pain Score Immediately Following Injection[7]



¶*P*<.0001; based on VAS 0-100

‡Same active ingredient

§Vs original formulation; immediately after injection; based on VAS 0-100

Simple transition to Taltz Citrate-Free[4]

- **No new National Drug Codes (NDCs)**
- **No new Rx needed for existing Taltz patients**
- **No new PAs to transition existing Taltz patients**
- **No gaps in therapy**

Once inventory of Taltz original formulation is depleted,
Only citrate-free formulation will be available

VAS=Visual Analogue Scale; LSM=least squares mean; PA=prior authorization.

Taltz Citrate-Free Bioequivalence Study Design[7]
The Citrate-Free Bioequivalence Study (N=245) was a 2-arm, subject-blind, parallel-design study in healthy subjects age 18-75 years to evaluate bioequivalence of Taltz citrate-free (CF) formulation compared to the original formulation of Taltz. Subjects were stratified into 1 of 3 weight categories (low: <70.0 kg; medium: 70.0-80.0 kg; high: >80.0 kg). Participants were then randomized within the 3 weight categories 1:1 to a single subcutaneous dose of either 80 mg Taltz original formulation (n=126) or 80 mg Taltz CF formulation (n=119). Subjects in each group were sub-randomized 1:1:1 to injection site (arm, thigh, or abdomen). Injections were administered by a medical professional using an autoinjector. The primary endpoint was bioequivalence as measured by maximum concentration (Cmax) of serum ixekizumab and area under the concentration versus time curve (AUC) of ixekizumab from time of injection through day 85 and time of injection through infinity.

Taltz Citrate-Free Injection Pain Study Design[7]
Citrate-Free Injection Pain Study (N=70) was a subject-blind, randomized, crossover study in healthy subjects age 18-75 years to determine injection site pain differences between Taltz citrate-free formulation compared to the original formulation of Taltz. The primary endpoint was pain intensity on injection, as measured by VAS Pain 0-100. Subjects were randomized 1:1:1 to receive a single 1 mL subcutaneous injection of 80 mg Taltz original formulation, 80 mg Taltz citrate-free formulation 1 (CF1), or 80 mg Taltz citrate-free formulation 2 (CF2) in 1 of 3 possible treatment sequences on Days 1, 8, and 15 in a 3-period cross-over design. Injections were administered in the abdomen by a medical professional using a prefilled syringe. CF2 is not an approved formulation. Only data on the commercially available CF1 will be presented.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

Taltz is **indicated** for adult patients with active ankylosing spondylitis, for adult patients with active psoriatic arthritis (PsA), and for adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. Taltz is also **indicated** for adult patients and pediatric patients aged 6 years or older with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

Taltz is contraindicated in patients with a previous serious hypersensitivity reaction, such as anaphylaxis, to ixekizumab or to any of the excipients.

WARNINGS AND PRECAUTIONS

Infections
Taltz may increase the risk of infection. In clinical trials of adult patients with plaque psoriasis, the Taltz group had a higher rate of infections than the placebo group (27% vs 23%). A similar increase in risk of infection was seen in placebo-controlled trials of adult patients with psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and pediatric patients with plaque psoriasis. Serious infections have occurred. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue Taltz until the infection resolves.

Pre-Treatment Evaluation for Tuberculosis
Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with Taltz. Do not administer to patients with active TB infection. Initiate treatment of latent TB prior to administering Taltz. Closely monitor patients receiving Taltz for signs and symptoms of active TB during and after treatment.

Hypersensitivity
Serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), occurred in the Taltz group in clinical trials. Anaphylaxis, including cases leading to hospitalization, has been reported in post-marketing use with Taltz. If a serious hypersensitivity reaction occurs, discontinue Taltz immediately and initiate appropriate therapy.

Inflammatory Bowel Disease
Patients treated with Taltz may be at an increased risk of inflammatory bowel disease. In clinical trials, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the Taltz group than the placebo group. During Taltz treatment, monitor patients for onset or exacerbations of inflammatory bowel disease and if IBD occurs, discontinue Taltz and initiate appropriate medical management.

Immunizations
Prior to initiating therapy with Taltz, consider completion of all age-appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with Taltz.

ADVERSE REACTIONS

Most common adverse reactions (≥1%) associated with Taltz treatment are injection site reactions, upper respiratory tract infections, nausea, and tinea infections. Overall, the safety profiles observed in adult patients with psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and pediatric patients with plaque psoriasis were consistent with the safety profile in adult patients with plaque psoriasis, with the exception of influenza and conjunctivitis in psoriatic arthritis and conjunctivitis, influenza, and urticaria in pediatric psoriasis.

Please see Brief Summary of Prescribing Information on the following pages. Please see Instructions for Use included with the device.

IX HCP ISI 07MAY2020

References: 1. Data on file. Lilly USA, LLC. DOF-IX-US-0304. **2.** Mease PJ, van der Heijde D, Ritchlin CT, et al; on behalf of SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis.* 2017;76:79-87. **3.** Nash P, Kirkham B, Okada M, et al; on behalf of SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet.* 2017;389:2317-2327. **4.** Taltz. Prescribing information. Lilly, USA. LLC. **5.** Mease PJ, van der Heijde D, Ritchlin CT, et al; on behalf of SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase 3 trial SPIRIT-P1. *Ann Rheum Dis.* 2017;76(suppl):1-30. **6.** Nash P, Kirkham B, Okada M, et al; on behalf of SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet.* 2017;389:2317-2327. Supplementary appendix. **7.** Chabra S, Gill BJ, Gallo G, et al. Ixekizumab citrate-free formulation: results from two clinical trials. *Adv Ther.* 2022;Epub (Incl Suppl Inf):1-11, 1-4. https://doi.org/10.1007/s12325-022-02126-0.

Taltz® (ixekizumab) injection

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

Plaque Psoriasis—Taltz is indicated for the treatment of patients aged 6 years and older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis—Taltz is indicated for the treatment of adult patients with active psoriatic arthritis.

Ankylosing Spondylitis—Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis.

Non-radiographic Axial Spondyloarthritis—Taltz is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

CONTRAINDICATIONS

Taltz is contraindicated in patients with a previous serious hypersensitivity reaction, such as anaphylaxis, to ixekizumab or to any of the excipients *(Warnings and Precautions)*.

WARNINGS AND PRECAUTIONS

Infections—Taltz may increase the risk of infection. In clinical trials in adult patients with plaque psoriasis, the Taltz group had a higher rate of infections than the placebo group (27% vs 23%). Upper respiratory tract infections, oral candidiasis, conjunctivitis and tinea infections occurred more frequently in the Taltz group than in the placebo group. A similar increase in risk of infection was seen in placebo-controlled trials in patients with pediatric psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis *(Adverse Reactions)*.
Instruct patients treated with Taltz to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy, monitor the patient closely and discontinue Taltz until the infection resolves.

Pre-treatment Evaluation for Tuberculosis—Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with Taltz. Do not administer to patients with active TB infection. Initiate treatment of latent TB prior to administering Taltz. Consider anti-TB therapy prior to initiating Taltz in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving Taltz should be monitored closely for signs and symptoms of active TB during and after treatment.

Hypersensitivity—Serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), occurred in the Taltz group in clinical trials. Anaphylaxis, including cases leading to hospitalization, has been reported in post-marketing use with Taltz *(Adverse Reactions)*. If a serious hypersensitivity reaction occurs, discontinue Taltz immediately and initiate appropriate therapy.

Inflammatory Bowel Disease—Patients treated with Taltz may be at an increased risk of inflammatory bowel disease. In clinical trials, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the Taltz group than in the control group *(Adverse Reactions)*. During Taltz treatment, monitor for onset or exacerbation of inflammatory bowel disease and if IBD occurs, discontinue Taltz and initiate appropriate medical management.

Immunizations—Prior to initiating therapy with Taltz, consider completion of all age-appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with Taltz. No data are available on the response to live vaccines.

ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Infections *(Warnings and Precautions)*
- Hypersensitivity Reactions *(Contraindications* and *Warnings and Precautions)*
- Inflammatory Bowel Disease *(Warnings and Precautions)*

Clinical Trials Experience—Because clinical trials are conducted under widely varying and controlled 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.

Adult Plaque Psoriasis

Weeks 0 to 12: Three placebo-controlled trials in subjects with plaque psoriasis were integrated to evaluate the safety of Taltz compared to placebo for up to 12 weeks. A total of 1167 subjects (mean age 45 years; 66% men; 94% White) with plaque psoriasis received Taltz (160 mg at Week 0, 80 mg every 2 weeks [Q2W] for 12 weeks) subcutaneously. In two of the trials, the safety of Taltz (use up to 12 weeks) was also compared with an active comparator, U.S. approved etanercept.

In the 12-week, placebo-controlled period, adverse events occurred in 58% of the Taltz Q2W group (2.5 per subject-year of follow-up) compared with 47% of the placebo group (2.1 per subject-year of follow-up). Serious adverse events occurred in 2% of the Taltz group (0.07 per subject-year of follow-up), and in 2% of the placebo group (0.07 per subject-year of follow-up). Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the Taltz group than the placebo group during the 12-week placebo-controlled period of the pooled clinical trials.

Table 1: Adverse Reactions Occurring in ≥1% of the Taltz Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Clinical Trials through Week 12

Adverse Reactions	Taltz 80 mg Q2W (N=1167) (n%)	Etanercept[b] (N=287) (n%)	Placebo (N=791) (n%)
Injection site reactions	196 (17)	32 (11)	26 (3)
Upper respiratory tract infections[a]	163 (14)	23 (8)	101 (13)
Nausea	23 (2)	1 (<1)	5 (1)
Tinea infections	17 (2)	0	1 (<1)

[a] Upper respiratory tract infections cluster includes nasopharyngitis and rhinovirus infection.
[b] U.S. approved etanercept.

Adverse reactions that occurred at rates less than 1% in the Taltz group and more frequently than in the placebo group during the 12-week induction period included rhinitis, oral candidiasis, urticaria, influenza, conjunctivitis, inflammatory bowel disease, and angioedema.

Weeks 13 to 60: A total of 332 subjects received the recommended maintenance regimen of Taltz 80 mg dosed every 4 weeks. During the maintenance period (Weeks 13 to 60), adverse events occurred in 80% of subjects treated with Taltz (1.0 per subject-year of follow-up) compared to 58% of subjects treated with placebo (1.1 per subject-year of follow-up). Serious adverse events were reported in 4% of subjects treated with Taltz (0.05 per subject-year of follow-up) and none in the subjects treated with placebo.

Weeks 0 to 60: Over the entire treatment period (Weeks 0 to 60), adverse events were reported in 67% of subjects treated with Taltz (1.4 per subject-year of follow-up) compared to 48% of subjects treated with placebo (2.0 per subject-year of follow-up). Serious adverse events were reported in 3% of subjects treated with Taltz (0.06 per subject-year of follow-up), and in 2% of subjects treated with placebo (0.06 per subject-year of follow-up).

Specific Adverse Drug Reactions**:**

Injection Site Reactions: The most frequent injection site reactions were erythema and pain. Most injection site reactions were mild-to-moderate in severity and did not lead to discontinuation of Taltz.

Infections: In the 12-week, placebo-controlled period of the clinical trials in plaque psoriasis, infections occurred in 27% of subjects treated with Taltz (1.2 per subject-year of follow-up) compared to 23% of subjects treated with placebo (1.0 per subject-year of follow-up). Serious infections occurred in 0.4% of subjects treated with Taltz (0.02 per subject-year of follow-up) and in 0.4% of subjects treated with placebo (0.02 per subject-year of follow-up) *(Warnings and Precautions)*.

During the maintenance treatment period (Weeks 13 to 60), infections occurred in 57% of subjects treated with Taltz (0.70 per subject-year of follow-up) compared to 32% of subjects treated with placebo (0.61 per subject-year of follow-up). Serious infections occurred in 0.9% of subjects treated with Taltz (0.01 per subject-year of follow-up) and none in the subjects treated with placebo.

Over the entire treatment period (Weeks 0 to 60), infections were reported in 38% of subjects treated with Taltz (0.83 per subject-year of follow-up) compared to 23% of subjects treated with placebo (1.0 per subject-year of follow-up). Serious infections occurred in 0.7% of subjects treated with Taltz (0.02 per subject-year of follow-up), and in 0.4% of subject treated with placebo (0.02 per subject-year of follow-up).

*Inflammatory Bowel Disease: I*n adult subjects with plaque psoriasis, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the TALTZ 80 mg Q2W group (Crohn's disease 0.1%, ulcerative colitis 0.2%) than the placebo group (0%) during the 12-week, placebo-controlled period in clinical trials *(Warnings and Precautions).*

Laboratory Assessment of Cytopenia:

Neutropenia—Over the entire treatment period (Weeks 0 to 60), neutropenia occurred in 11% of subjects treated with Taltz (0.24 per subject-year of follow-up) compared to 3% of subjects treated with placebo (0.14 per subject-year of follow-up). In subjects treated with Taltz, the incidence rate of neutropenia during Weeks 13 to 60 was lower than the incidence rate during Weeks 0 to 12.

In the 12-week, placebo-controlled period, neutropenia ≥ Grade 3 (<1,000 cells/mm^3) occurred in 0.2% of the Taltz group (0.007 per subject-year of follow-up) compared to 0.1% of the placebo group (0.006 per subject-year of follow-up). The majority of cases of neutropenia were either Grade 2 (2% for Taltz 80 mg Q2W versus 0.3% for placebo; ≥1,000 to <1,500 cells/mm^3) or Grade 1 (7% for Taltz 80 mg Q2W versus 3% for placebo; ≥1,500 cells/mm^3 to <2,000 cells/mm^3). Neutropenia in the Taltz group was not associated with an increased rate of infection compared to the placebo group.

Thrombocytopenia—Ninety eight percent of cases of thrombocytopenia were Grade 1 (3% for Taltz 80 mg Q2W versus 1% for placebo; ≥75,000 cells/mm^3 to <150,000 cells/mm^3). Thrombocytopenia in subjects treated with Taltz was not associated with an increased rate of bleeding compared to subjects treated with placebo.

Active Comparator Trials: In the two clinical trials that included an active comparator, the rate of serious adverse events during weeks zero to twelve was 0.7% for U.S.-approved etanercept and 2% for Taltz 80 mg Q2W, and the rate of discontinuation from adverse events was 0.7% for U.S. approved etanercept and 2% for Taltz 80 mg Q2W. The incidence of infections was 18% for U.S. approved etanercept and 26% for Taltz 80 mg Q2W. The rate of serious infections was 0.3% for both Taltz 80 mg Q2W and U.S. approved etanercept.

Pediatric Plaque Psoriasis

Taltz was evaluated in a placebo-controlled trial in pediatric subjects with moderate-to-severe psoriasis 6 to less than 18 years of age. A total of 171 subjects were studied (115 subjects on Taltz and 56 subjects on placebo). Overall, the safety profile observed in pediatric subjects with plaque psoriasis treated with Taltz every 4 weeks is consistent with the safety profile in adult subjects with plaque psoriasis with the exception of the frequencies of conjunctivitis (2.6%), influenza (1.7%), and urticaria (1.7%).

In this clinical trial, Crohn's disease occurred at a greater frequency in the Taltz group (0.9%) than the placebo group (0%) during the 12-week, placebo-controlled period. Crohn's disease occurred in a total of 4 Taltz treated subjects (2.0%) in the clinical trial *(Warnings and Precautions).*

Psoriatic Arthritis

Taltz was studied in two placebo-controlled trials in patients with psoriatic arthritis. A total of 678 patients were studied (454 patients on Taltz and 224 on placebo). A total of 229 patients in these trials received Taltz 160 mg at Week 0, followed by 80 mg every 4 weeks (Q4W). Overall, the safety profile observed in patients with psoriatic arthritis treated with Taltz Q4W is consistent with the safety profile in adult patients with plaque psoriasis with the exception of the frequencies of influenza (1.3%) and conjunctivitis (1.3%).

Taltz® (ixekizumab) injection IX HCP BS 06JAN2022

Ankylosing Spondylitis

Taltz was studied in two placebo-controlled trials in patients with ankylosing spondylitis. A total of 566 patients were studied (376 patients on Taltz and 190 on placebo). A total of 195 patients in these trials received Taltz 80 or 160 mg at Week 0, followed by 80 mg every 4 weeks (Q4W). Overall, the safety profile observed in patients with ankylosing spondylitis treated with Taltz Q4W is consistent with the safety profile in adult patients with plaque psoriasis.

In adult patients with ankylosing spondylitis, Crohn's disease and ulcerative colitis, including exacerbations, occurred in 2 patients (1.0%) and 1 patient (0.5%), respectively, in the Taltz 80 mg Q4W group and 1 patient (0.5%) and 0%, respectively, in the placebo group during the 16-week, placebo-controlled period in clinical trials. Of these patients, serious events occurred in 1 patient in the Taltz 80 mg Q4W group and 1 patient in the placebo group *(Warnings and Precautions).*

Non-radiographic Axial Spondyloarthritis

Taltz was studied in a placebo-controlled trial in patients with non-radiographic axial spondyloarthritis. A total of 303 patients were studied (198 patients on Taltz and 105 on placebo). A total of 96 patients in this trial received Taltz 80 or 160 mg at Week 0, followed by 80 mg every 4 weeks (Q4W). Overall, the safety profile observed in patients with non-radiographic axial spondyloarthritis treated with Taltz 80 mg Q4W up to Week 16 is consistent with the previous experience of Taltz in other indications.

Immunogenicity—As with all therapeutic proteins, there is the potential for immunogenicity with Taltz. The assay to test for neutralizing antibodies has limitations detecting neutralizing antibodies in the presence of ixekizumab; therefore, the incidence of neutralizing antibodies development could be underestimated.

Plaque Psoriasis Population

By Week 12, approximately 9% of adult subjects treated with Taltz every 2 weeks developed antibodies to ixekizumab. Approximately 22% of subjects treated with Taltz at the recommended dosing regimen developed antibodies to ixekizumab during the 60-week treatment period. The clinical effects of antibodies to ixekizumab are dependent on the antibody titer; higher antibody titers were associated with decreasing drug concentration and clinical response.

Of the adult subjects who developed antibodies to ixekizumab during the 60-week treatment period, approximately 10%, which equates to 2% of subjects treated with Taltz at the recommended dosing regimen, had antibodies that were classified as neutralizing. Neutralizing antibodies were associated with reduced drug concentrations and loss of efficacy.

In pediatric psoriasis subjects treated with ixekizumab at the recommended dosing regimen up to 12 weeks, 21 subjects (18%) developed anti-drug antibodies, 5 subjects (4%) had confirmed neutralizing antibodies associated with low drug concentrations. No conclusive evidence could be obtained on the potential association of neutralizing antibodies and clinical response and/or adverse events due to small number of pediatric subjects in the study.

Psoriatic Arthritis Population

For subjects treated with Taltz 80 mg every 4 weeks for up to 52 weeks (PsA1), 11% developed anti-drug antibodies, and 8% had confirmed neutralizing antibodies.

Ankylosing Spondylitis Population

For patients treated with Taltz 80 mg every 4 weeks for up to 16 weeks (AS1, AS2), 5.2% developed anti-drug antibodies, and 1.5% had neutralizing antibodies.

Non-radiographic Axial Spondyloarthritis Population

Of patients treated with Taltz 80 mg every 4 weeks for up to 52 weeks (nr-axSpA1), 8.9% developed anti-drug antibodies, all of which were low titer. No patient had neutralizing antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to Taltz across indications or with the incidences of antibodies to other products may be misleading.

Postmarketing Experience—The following adverse reactions have been identified during post-approval use of Taltz. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Taltz exposure.

Immune system disorders: anaphylaxis *(Contraindications* and *Warnings and Precautions)*

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Taltz during pregnancy. Pregnant women should be encouraged to enroll themselves in the registry by calling 1-800-284-1695.

Risk Summary—There are no available data on Taltz use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, Taltz may be transmitted from the mother to the developing fetus. An embryofetal development study conducted in pregnant monkeys at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus. When dosing was continued until parturition, neonatal deaths were observed at 1.9 times the MRHD *[see Data]*. The clinical significance of these nonclinical findings is unknown.

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.

Data

Animal Data—An embryofetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis to near parturition at doses up to 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). These neonatal deaths were attributed to early delivery, trauma, or congenital defect. The clinical significance of these findings is unknown. No ixekizumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

Lactation

Risk Summary—There are no data on the presence of ixekizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Taltz and any potential adverse effects on the breastfed infant from Taltz or from the underlying maternal condition.

Pediatric Use—The safety and effectiveness of Taltz have been established in pediatric subjects aged 6 years to less than 18 years with moderate-to-severe plaque psoriasis. The safety and effectiveness of Taltz in other pediatric indications and for pediatric subjects less than 6 years of age have not been established.

Geriatric Use—Of the 4204 psoriasis subjects exposed to Taltz, a total of 301 were 65 years or older, and 36 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

PATIENT COUNSELING INFORMATION—Advise the patient and/or caregiver to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before the patient starts using Taltz and each time the prescription is renewed, as there may be new information they need to know.

Instructions on Self-Administration: Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the autoinjector or prefilled syringe correctly *(Instructions for Use)*.

Infection: Inform patients that Taltz may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider, and contacting their healthcare provider if they develop any symptoms of infection *(Warnings and Precautions).*

Allergic Reactions: Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *(Warnings and Precautions).*

Pregnancy: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Taltz during pregnancy. Advise patients to contact the registry at 1-800-284-1695 to enroll (*Use in Specific Populations)*.

Additional information can be found at www.Taltz.com.

See Instructions for Use accompanying the product device.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

IX HCP BS 06JAN2022

PP-IX-US-5359

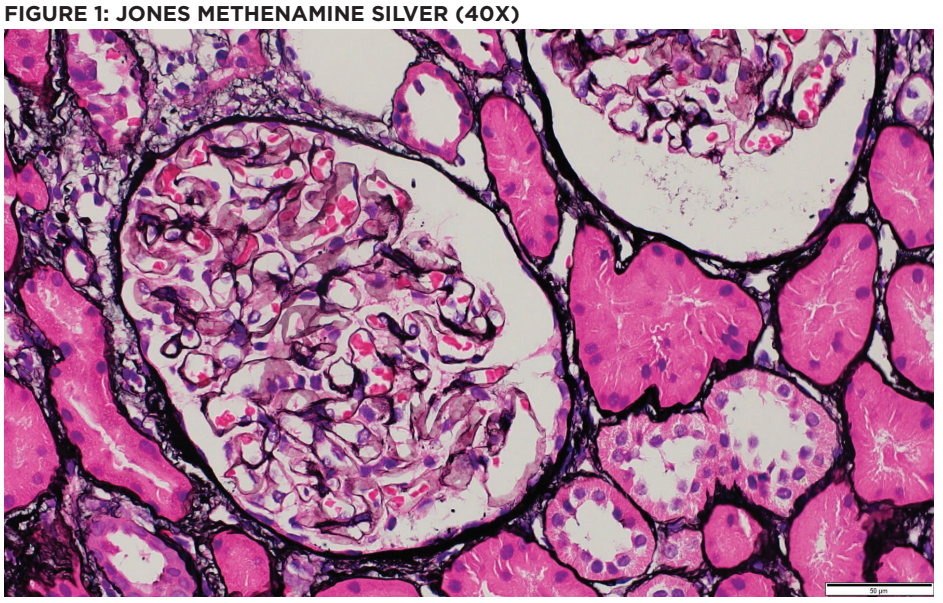
Taltz® (ixekizumab) injection IX HCP BS 06JAN2022

Dx: Lupus Nephritis?

Co-infection with syphilis & parvovirus B19 mimicking lupus nephritis

BY MATTHEW J. MANDELL, DO, YISHUI CHEN, MD, PRERNA RASTOGI, MD, PHD, & REBECCA TUETKEN, MD, PHD

FIGURE 1: JONES METHENAMINE SILVER (40X)



Segmental spikes and holes noted in glomerular capillary loops.

The diagnosis of lupus nephritis should be questioned when serologic & other laboratory markers & clinical manifestations of lupus are absent despite suggestive renal histology findings.

Syphilis, an ancient disease caused by the spirochete *Treponema pallidum*, has been historically referred to as the *great mimicker* given its heterogenous presentation. Both systemic lupus erythematosus (SLE) and syphilis can have multi-systemic involvement. Both parvovirus B19 and syphilis have been reported to cause histologic features similar to those seen in lupus nephritis.

We present a case in which co-infection with syphilis and parvovirus B19 could have been mistaken for lupus nephritis. We highlight clinical features to help differentiate between lupus nephritis and nephrotic syndrome caused by co-infection with syphilis and parvovirus B19. Making the correct diagnosis has important implications: Nephrotic syndrome associated with parvovirus B19 often improves spontaneously and that with syphilis improves with penicillin, whereas lupus nephritis requires systemic immunosuppression.

Case Presentation

A 34-year-old Angolese man presented with lower extremity edema, headache, malaise, arthralgias, rash, diarrhea and chest pain of six weeks' duration. He previously was evaluated at an urgent care clinic and was prescribed an oral non-steroidal anti-inflammatory drug for chest pain and myalgias, with symptomatic improvement. Renal biopsy was concerning for classes II and V lupus nephritis, for which a rheumatologist was consulted.

His creatinine was 1.4 mg/dL (reference range [RR] 0.75–1.20 mg/dL for men) on admission. Liver function tests were normal, except for an isolated elevation in alkaline phosphatase confirmed to be of hepatic etiology, with a corresponding elevation in gamma-glutamyl transferase.

The patient had recently been diagnosed with syphilis and treated with intramuscular penicillin a few weeks prior to his admission. His medical history included a prior diagnosis of COVID-19 and a remote history of malaria. Neither he nor his family had any history of autoimmune disease. He had not been taking any regular medications prior to admission. He denied use of illicit substances and had no travel outside the U.S. in several years. He reported being sexually active with male partners.

On admission to our hospital, his exam revealed prominent bilateral axillary and bilateral inguinal lymph nodes, soft tissue swelling in both ankles and pretibial pitting edema. Examination found no appreciable rashes on the skin, including a normal genital exam with no ulcerative lesions. The patient denied malar rash, photosensitivity, Raynaud's phenomenon, history of venous thromboembolic events, dry mouth, dry eye, history of seizure or stroke, history of cytopenias, nasal or oral ulcers, or hair loss.

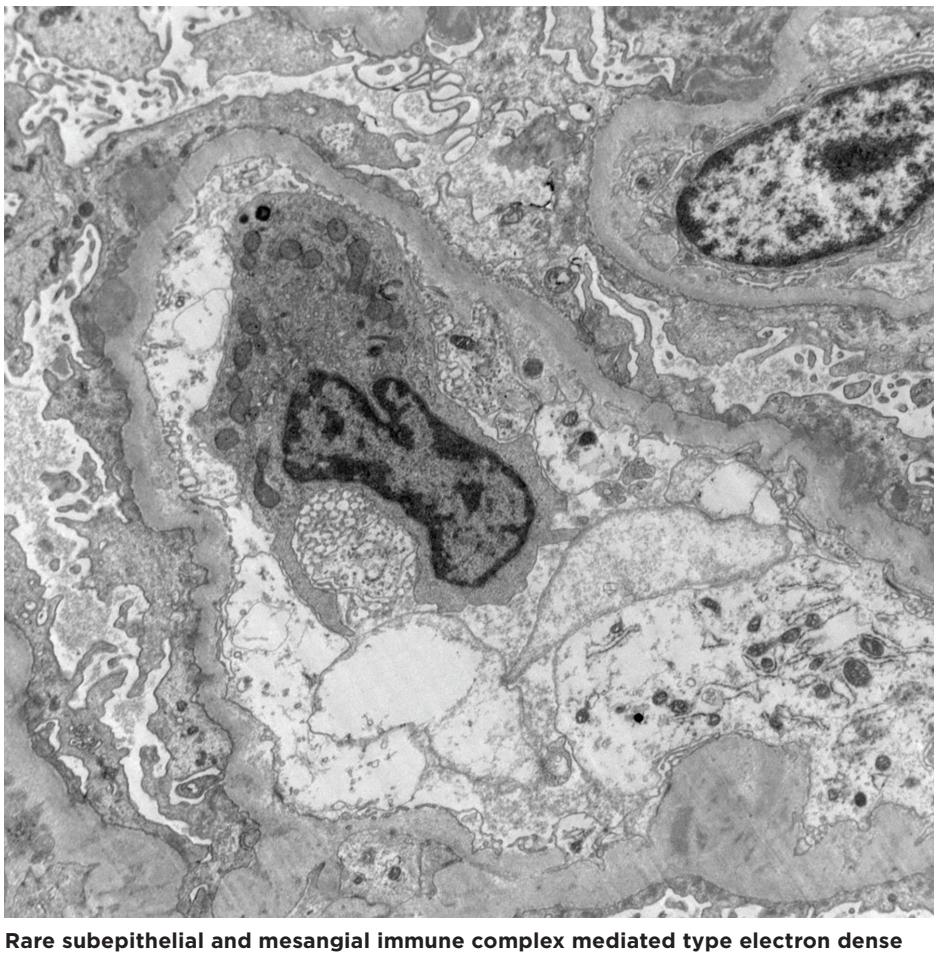
Initial urinalysis several weeks prior to admission showed 2–3+ protein, 2+ blood, and no casts. Proteinuria was quantified with random urine-to-protein-creatinine ratio, which was elevated at 5.65 g/g Cr. The ANA titer was 1:640 in nuclear coarse speckled pattern; tests for anti-Smith and double-stranded DNA antibodies were negative.

Serum complements were not low. A test for phospholipase A2 receptor (PLA2R) antibody was negative. Tests for human immunodeficiency virus (HIV) antigen and antibody, hepatitis B surface antigen and antibody, and hepatitis C antibody were negative. A test for RPR was positive (1:256), with a positive confirmatory syphilis total antibody test. Chlamydia and gonorrhea polymerase chain reaction testing returned negative. Tests for anti-phospholipid antibodies were negative.

The complete blood count test with differential was normal. Ferritin (408 ng/mL; RR: 12–300 ng/mL for men) and erythrocyte sedimentation rate (ESR) (56 mm/Hr; RR: 0–15 mm/Hr) were elevated; C-reactive protein (CRP) was just above the upper limit of normal (0.6 mg/dL; RR: <0.5 mg/dL).

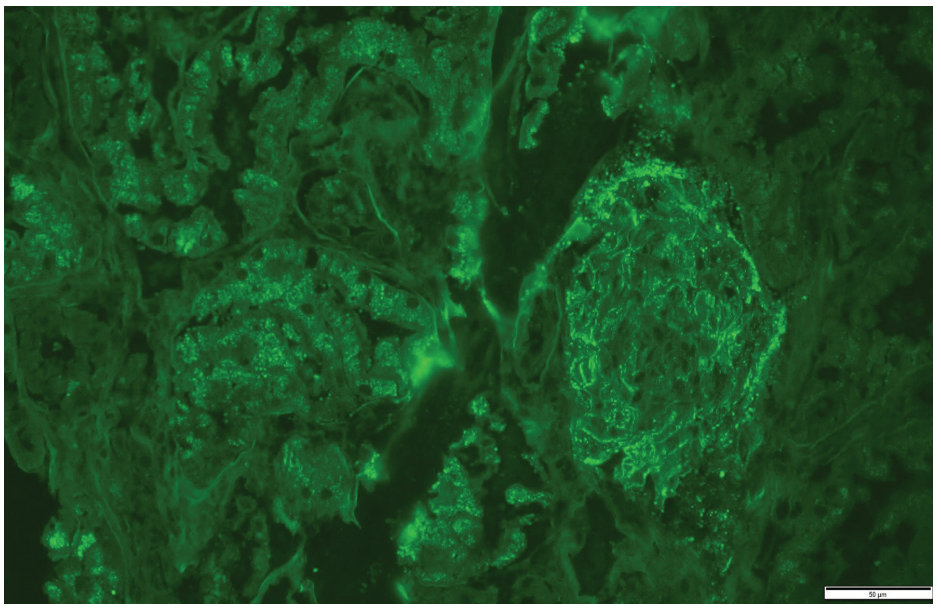
Liver function tests revealed hypoalbuminemia (1.9 g/dL) and elevated alkaline phosphatase (413 U/L; RR: <129 U/L) and gamma-glutamyl transferase (872 U/L; RR: <61 U/L). Serum parvovirus B19 IgG (1.16 IV; RR: <0.90 IV) and IgM (1.97 IV; RR: <0.90 IV) were consistent with recently acquired infection.

FIGURE 2: ELECTRON MICROSCOPY



Rare subepithelial and mesangial immune complex mediated type electron dense deposits present. Moderate podocyte epithelial foot process effacement is shown.

FIGURE 3: IMMUNOFLUORESCENCE IgG STAIN



IgG stain is positive in a granular pattern along capillary loop and rare mesangial areas.

A renal biopsy was suggestive of classes II and V lupus nephritis; however, no crescents were identified (see Figure 1, opposite). Renal biopsy showed a combined (segmental) membranous and minimal mesangial pattern of glomerulonephritis with negative PLA2R antibody stain (see Figure 2, opposite). On immunofluorescence, glomeruli showed segmental, capillary loop and full-house pattern (positive for IgG, IgM, IgA, C3, C1q) co-staining (see Figures 3 and 4, this page). Spirochete stain was negative on immunohistochemistry.

Given the presence of persistent headache, along with neck tenderness and positive syphilis testing, a lumbar puncture with cerebrospinal fluid analysis was performed, which revealed normal cell count, negative gram stain, normal glucose and negative venereal disease research laboratory test.

Patient presented with nephrotic syndrome (i.e., nephrotic range: proteinuria, elevated cholesterol and edema), which improved during his hospitalization. He was treated with 30 mg of lisinopril daily and 40 mg of atorvastatin daily.

At his one-month outpatient follow-up, his edema, headache, arthralgias, malaise, rash and diarrhea had all resolved. His cholesterol had normalized with statin therapy. Repeat urinalysis showed no blood and no protein, and the random urine-to-protein-creatine ratio had completely normalized (0.08 g/g Cr). His serum creatine declined to 1.2 mg/dL. His inflammatory markers had also completely normalized (ESR 1 and CRP <0.5 mg/dL), as had his alkaline phosphatase and albumin.

Discussion

Searching PubMed, we identified only one case of co-infection with syphilis and parvovirus B19 mimicking lupus nephropathy, as in our patient.[1] Parvovirus B19 and especially syphilis have been reported to cause the same histologic features of lupus nephritis—or so-called *pseudo-lupus nephritis*. Although the presence of C1q deposits is nearly pathognomonic for lupus nephritis, it can also be seen when parvovirus B19 causes kidney disease.[1]

Our patient's positive ANA and full-house pattern on renal biopsy pointed toward lupus nephritis; however, the discordant findings of negative double-stranded DNA and anti-Smith antibodies, lack of cytopenias, normal complements and lack of other clinical features of systemic lupus erythematosus made us question the diagnosis.

Syphilis fit the clinical schema well—and it should be noted that our patient's mild hepatitis, with isolated elevation of alkaline phosphatase, is very characteristic of syphilitic hepatitis.[2] The presence of C1q deposition in the kidney prompted us to check for parvovirus B19 antibodies, which came back suggestive of acute infection. This likely explained his symptoms of malaise and arthralgias, as well as skin redness/rash (which was not appreciated on admission when we evaluated the patient, several weeks after symptom onset). Other masqueraders of lupus nephritis include HIV and infective endocarditis.

Syphilis has been historically referred to as the *great mimicker* given its heterogenous presentation.[3,4] The three stages of infection are: primary, secondary and tertiary. Our patient likely had secondary infection, with rash and lymphadenopathy. Renal involvement can occur at any stage, from secondary to latent and tertiary. Both SLE and syphilis can have multisystem involvement.

This case illustrates the importance of thinking about infectious etiologies for glomerulonephritis and completing a thorough sexual history. Further, the diagnosis of lupus nephritis should be questioned when serologic and other laboratory markers (e.g., anti-Smith and double-stranded DNA antibodies, low complement levels, cytopenias) and clinical manifestations of lupus are absent, despite suggestive renal histology findings. The presence of C1q is nearly pathognomonic for lupus nephritis, but can also be seen when parvovirus B19 causes kidney disease.[1] Parvovirus B19 and syphilis have been reported to cause the same histologic features of lupus nephritis. [1,3,4-6]

In Sum

It's important to recognize the above etiologies of membranous nephropathy because the correct diagnosis has treatment implications. The nephrotic syndrome associated with parvovirus B19 infection may improve spontaneously and that with syphilis improves with penicillin.[3,5-7] A similar case of co-infection with both parvovirus B19 and syphilis improved with antibiotic treatment for syphilis.[1] R

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Rebecca Tuetken, MD, PhD, is a clinical professor of internal medicine (immunology), medical director of the Medical Specialty Clinic, and director of the rheumatology fellowship program at the University of Iowa Hospitals & Clinics.

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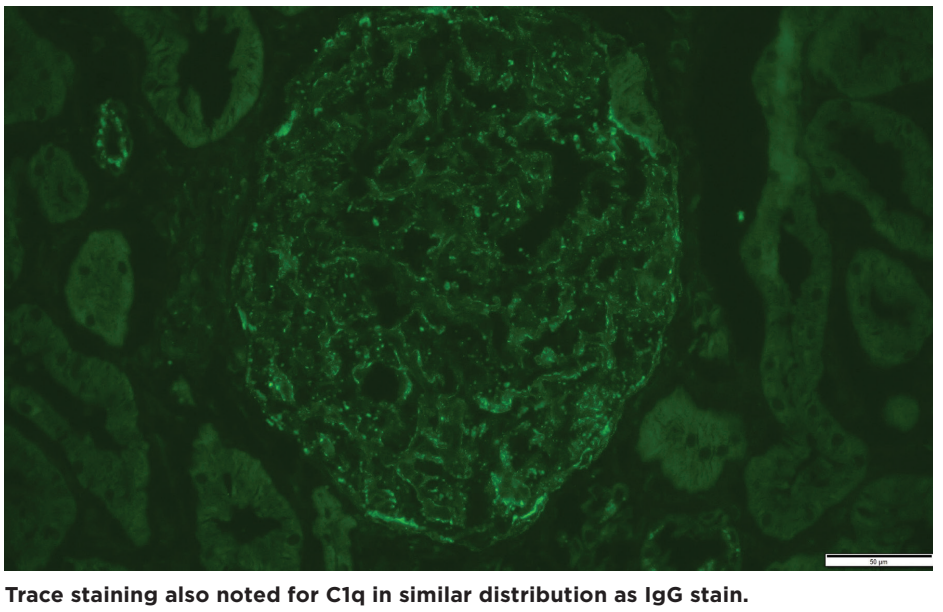
FIGURE 4: IMMUNOFLUORESCENCE C1Q STAIN



Trace staining also noted for C1q in similar distribution as IgG stain.

MEDICAL MISSION TO UKRAINE

Rheumatologist organizes mission to help Ukrainians displaced by Russian invasion

BY CATHERINE KOLONKO

DR. RACKOFF

> Many of the refugees needed medications to treat hypertension, diabetes, back pain, insomnia & common ailments. Dr. Rackoff also devoted a day in Krakow to treat people with osteoarthritis, cutaneous vasculitis & other rheumatic-related conditions.

Early in 2022, a few months into the invasion of Ukraine by Russian troops, Paula Rackoff, MD, a rheumatologist and clinical associate professor at NYU Grossman School of Medicine, New York, felt an urgency to head to the region to assist the many refugees fleeing for the border with Poland.

Dr. Rackoff canceled a planned bike trip in Croatia with friends and family and pulled together a small group of volunteers, including three other doctors. Initially, the relief organizations she reached out to said they had enough doctors and thanked her for her interest.

Then Dr. Rackoff contacted the Israeli crisis relief group One Heart. It had already sent young adults to hand out blankets and sandwiches, carry suitcases and generally help refugees cross from Ukraine into Poland, she says.

"When I heard about them I emailed the director, and I said why don't you send doctors. He said, 'Okay,'" recalls Dr. Rackoff. "Basically, it was an organization that said 'Yes,' so he said, 'Let's do it.'"

The dean of the medical school, Robert Grossman, MD, agreed to donate essential medications for the initial 10-day mission. Dr. Rackoff also felt the support of her colleagues, including one doctor who asked to cover for her while she was away on the volunteer mission.

"It was really 'yes' all along the way," she says. "I went twice, for 10 days each time."

On the Ground

Instead of the two wheels of a bicycle, Dr. Rackoff landed in Europe with several duffel bags full of medications that might be needed by Ukrainians who arrived at the Polish border with the few possessions they could carry. With four doctors on the first mission, the group saw about 400 patients a week, she says.

"We went to a refugee site outside Krakow. Then we went to three refugee sites on the border of Poland and Ukraine, and then we went into Lviv, also to a refugee site there."

In Ukraine, the group traveled no farther east than Lviv, which Dr. Rackoff says seemed relatively safe, like any other European city.

"But I think that has to be judged week by week," she notes. "Their main statues were surrounded by steel and sandbags, but other than that we didn't see any damage at all."

The border crossing lines were not as long as in the very early days of the Russian invasion, says Dr. Rackoff. Some of the border traffic included people going back to Ukraine out of necessity or just because they missed being home.

"What was explained to me is that a lot of people depend on their own gardens for their food," she says. "So if they don't plant during the summer, they won't have [food to eat] during the winter."

The team of doctors attended to mostly women and children because men aged 18 to 60 years old were required to stay in Ukraine to support military efforts against Russian forces. Many of the refugees needed medications to treat hypertension, diabetes, back pain, insomnia and common ailments.

Dr. Rackoff also devoted a day in Krakow to treat people with osteoarthritis, cutaneous vasculitis and other rheumatic-related conditions. She recalls attending to one woman who had frozen shoulder.

"That's a difficult situation because there was no physical therapy, so I sort of showed her what to do and then eventually she was going to see an orthopedist," explains Dr. Rackoff.

"The refugees are not [that] sick, but they don't quite yet have access to medical care," she says. "I saw one woman who was in tears because she has breast cancer. A year ago, she knew she was in remission, but she can't get her scans. So it's heartbreaking."

One of the doctors and his teenage son, who also volunteered on the mission, speak Russian and served as the group's interpreters. This doctor had also been with Dr. Rackoff years earlier on a medical mission to Ghana.

The second visit included team members' teenage children, who came along to volunteer, and a nurse practitioner from NYU who heard about the mission and wanted to participate. That nurse was born in the former Soviet Union and speaks Russian, so she also served as an interpreter, says Dr. Rackoff.

Not Her First Rodeo

Over 25 years, Dr. Rackoff has traveled to many destinations on medical missions, including Nicaragua, South Africa, Israel and Palestine. Her daughter, Maya Rackoff, who was 11 when she accompanied her mother to Ghana, also went on this most recent trip to volunteer.

"It's always been a real passion of mine," says Dr. Rackoff about volunteer missions. "My daughter is a sophomore now in college, so I feel like I have a little more free time."

Dr. Rackoff plans to return to the Ukraine/Poland border again, probably in the winter. It would be her third visit since the Russian invasion, and interest among her colleagues continues to grow, she says.

The only other time Dr. Rackoff had been in Poland was in 1990 when she went there to honor her ancestors, visit memorial sites and learn more about the Holocaust. It was important to her that an Israeli organization, such as One Heart, sponsored her recent missions to Poland and Ukraine.

"Even though I had volunteered in different countries before, I had a particular connection to Poland and Ukraine because my great-grandparents came from there in the late 1800s," says Dr. Rackoff.

"It was very important for me personally to go with an Israeli group because of the history of the Holocaust there," she adds.

It's a connection she shares with other Jewish doctors with ancestors who experienced the atrocities of the Holocaust.

"That's where the origin of our families come from," says Dr. Rackoff. "So to show up, [and be] helping rather than being the victim is just very meaningful."

In the Moment

Reflecting on the missions to Poland and Ukraine, Dr. Rackoff says her experience was about meeting the moment when thousands of displaced people needed help from others who cared.

"There was this general feeling of we're really here to do the right thing in a very historic time," she says. R

Dr. Rackoff near the Ukraine border with duffel bags of medicine donated by NYU Langone Health.

Catherine Kolonko is a medical writer based in Oregon.

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Pocketbook vs. Treatment


DR. ALLMAN

Has the patient asked for more than can be ethically allowed?

BY RICHARD L. ALLMAN, MD, MS, FACP, FACR

The patient, a 76-year-old woman, had very active polyarticular rheumatoid arthritis (RA), despite triple therapy with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), low-dose corticosteroids and occasional intra-articular injections—the latter providing only transient symptomatic relief. She had elevated inflammatory markers and a 28-joint Disease Activity Score (DAS-28) score of 7.4.

Because of the severity of her disease, the next appropriate step in management was the addition of a biologic agent. After discussing the options with the patient and her daughter, etanercept, a tumor necrosis factor α (TNFα) blocker, was recommended. The patient and her daughter agreed, and preliminary tests were ordered to determine if it could be used safely.

When the patient and her daughter returned to review the laboratory studies and discuss use of the agent, the patient's daughter explained that the patient had an insurance plan with a substantial copay for biologic agents. The daughter requested that, instead, the prescription be written in her name; the daughter was well connected to the hospital and had a more robust prescription-reimbursement plan.

The patient's daughter was told this would not be possible, that there was no documentation that the daughter had rheumatoid arthritis—she had no preliminary laboratory studies—and that this would be fraudulent. Further, if by some chance the daughter were to take the medication on her own, adverse reactions might be possible from a medication neither indicated nor monitored.

The patient and her daughter were adamant that they wanted in-home subcutaneous options rather than infusions at an infusion center, which would have been covered under the patient's insurance. They were told the office could attempt to find out if the patient qualified for a manufacturer's discount or financial support, but neither the patient nor her daughter found that acceptable and left without scheduling a follow-up appointment.

Discussion

As a practical matter, a biologic agent cannot be prescribed appropriately without an established indication and evidence of failure to respond to lesser treatments, as well as with initial and ongoing monitoring. These factors alone precluded acceding to the patient's and daughter's request. The explanation offered to them was non-accusatory; however, even if such a prescription were possible, the ethical implications would be substantial.

Simply stated, medicine is a moral undertaking. As autonomous moral agents, patients have a right to competently accept or refuse diagnostic or therapeutic recommendations. That stated, the moral agency of physicians also must be respected. This means patients and their decision makers should not ask physicians to violate their conscience or the integrity of the profession. Engaging in a request to defraud a prescription reimbursement plan, even for the benefit of an underinsured patient, is beyond what should be asked or demanded.

This case illustrates the obstacles that underinsured patients confront, but the solution the patient and her daughter suggested was ethically indefensible.

Access to needed care and disparities in coverage are broad societal problems that demand the attention of ethical practitioners. The moral obligation for medicine as an organized moral community is to advocate for access to needed treatments for all our patients, both individually and collectively through our professional societies, and to explore options either through alternate insurers or through manufacturers' support programs, while preserving the honor of the profession as adhering to the highest ethical standards.

Some literature addresses the unsettled ethical landscape of "gaming the system" by altering assessments of disease severity to obtain third-party approval for beneficial interventions or changing the primary diagnosis for similar diagnostic and therapeutic benefits, practices that have have collectively been described as covert advocacy.[1]

Gaming the system is well intentioned for the patient's benefit, but ethically dubious. It entails deliberately misrepresenting a diagnosis or severity of illness to obtain reimbursement for a service that has medical benefit but is not covered by a patient's particular insurance contract.

All physicians likely have encountered patient requests for what seem like excessively long periods of disability from work, or requests for in-home services, which, while convenient, are not truly medically necessary, and requests for marginally necessary durable medical equipment, all of which skirt the edges of truthful documentation. Physicians have significant obligations to their patients: to be competent; to act in the interest of their patients, including through private and public advocacy; and to undertake acceptable risks for the benefit of their patients, the latter of which we have encountered during the long season of COVID-19. Nonetheless, there is no moral obligation to compromise our character or integrity, even in situations of regrettable denial of valuable service or medications.


TERO VESALAINEN / SHUTTERSTOCK.COM

Freeman et al. articulated concern about physician complicity with deliberate deception, including legal, contractual and ethical consequences:

> *Situations that produce deception can ultimately only be solved by direct confrontation and frank dialogue between physicians, patients and payers. Alternatives to deception include broadening existing appeals processes on behalf of individual patients and political advocacy for health care reform. Refusal to initiate a social dialogue regarding the appropriate balance between medical and economic considerations places medicine at risk of becoming a practice of equal parts patient care and subterfuge.*[2]

The case described is far beyond the bounds of gaming the system, but is a clear request for falsification of diagnosis to which the patient or her daughter have no moral standing to request the physician's complicity, and the physician is morally obligated to respectfully refuse. R

Richard L. Allman, MD, MS, FACP, FACR, was an associate director of the residency program in internal medicine at Einstein Medical Center, Philadelphia, from 2002–18. He has a Master of Science in Healthcare Ethics and continues to serve as the lead consultant in ethics at Einstein, while working part time to precept internal medicine residents.

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Editor's note: This article was written for *The Rheumatologist* on behalf of the ACR Committee on Ethics & Conflict of Interest. If you have a comment for the author or a case you'd like to see in Ethics Forum, email us at **klosavio@wiley.com**.

Belimumab Promising for Children with Lupus Nephritis

New hope for our young patients

■ BY MICHELE B. KAUFMAN, PharmD, BCGP

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In late July, the U.S. Food & Drug Administration (FDA) approved belimumab (Benlysta) for the treatment of children aged 5–17 years old with active lupus nephritis who are receiving standard therapy.[1] Despite recent advances in treatment options for patients with systemic lupus erythematosus (SLE), those with kidney involvement face the possibility of developing end-stage renal disease and needing subsequent hemodialysis or transplantation. Belimumab may improve the prognosis for pediatric patients with lupus.

The indications for the intravenous (IV) formulation of belimumab have been expanded to include pediatric patients with SLE, as well as those with active lupus nephritis.[2] The recommended dosing of IV belimumab for pediatric patients is 10 mg/kg every two weeks for the first three doses, with subsequent infusions given at four-week intervals.[3]

Background

The efficacy and safety of belimumab were evaluated for one year in a randomized, double-blind, placebo-controlled study (N=93; NCT01649765).[4] Similar to the clinical trials of belimumab in adults, enrolled pediatric patients had to have a clinical diagnosis of SLE according to the ACR classification criteria, active SLE (i.e., defined as a SELENA-SLEDAI score of at least 6) and the presence of autoantibodies at screening.

The researchers enrolled 93 pediatric patients aged 5 to 17 years who were on stable treatment regimens for their SLE (i.e., standard therapy) and had similar inclusion and exclusion criteria as participants in the clinical trials for adults. The standard therapy included corticosteroids, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs) and/or immunosuppressives, alone or in combination. Use of other biologics and IV cyclophosphamide was not allowed during the course of this study.

The median patient age was 15 years (range: 6–17 years), and most patients were female (95%). At baseline, more than half of the patients had active involvement of at least three organ systems, the most common of which were the mucocutaneous (91%), immunologic (74%) and musculoskeletal (73%). Nineteen percent of patients had some degree of kidney disease, with less than 7% of patients having their cardio-respiratory, hematologic, central nervous system or vascular systems affected. The study's primary efficacy end point was the SLE Responder Index (SRI-4) at week 52, as described in the adult trials of IV belimumab.

Results

Forty patients received placebo and standard therapy, and 53 patients received belimumab plus standard therapy. A higher proportion of patients receiving belimumab plus standard therapy achieved an SRI-4 response than patients who received placebo plus standard therapy (44% vs. 53%, odds ratio [OR]=1.49 [0.64, 3.46]).

At baseline, 95% of patients were receiving prednisone. Of the patients treated with belimumab plus standard therapy, no difference was found in the frequency of prednisone reduction between the belimumab- and placebo-treated groups (20.0% and 21%, respectively). This study was not designed or powered to assess a steroid-sparing effect.

The probability of having an SLE disease flare was measured by the modified SELENA-SLEDAI Flare Index. The proportion of patients reporting at least one severe flare during the study was lower in patients treated with belimumab plus standard therapy (17%) than in the proportion of patients treated with placebo plus standard therapy (35%). The addition of belimumab to standard therapies resulted in a 64% lower risk of experiencing a severe disease flare during the study than patients who received placebo plus standard therapy.

Of the patients who had a severe flare, the median time to the first severe flare was 150 days in patients receiving belimumab plus standard therapy and 113 days in patients receiving placebo plus standard therapy. This was a non-powered trial. In the 53 patients who received belimumab, no formation of anti-belimumab antibodies occurred.

In this patient population, belimumab's pharmacokinetics were consistent with those of the adult population with SLE. No new safety signals were identified. This FDA approval marks a significant step forward, providing treatment options for pediatric patients at risk of developing early renal damage and failure due to SLE. R

Michele B. Kaufman, PharmD, BCGP, is a freelance medical writer based in New York City and a pharmacist at New York Presbyterian Lower Manhattan Hospital.

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TAVNEOS® (AVACOPAN) CAPSULES FOR ORAL USE BRIEF SUMMARY OF THE FULL PRESCRIBING INFORMATION (PI) — RX ONLY

INDICATIONS AND USAGE

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

DOSAGE AND ADMINISTRATION

Recommended Evaluations Prior to Treatment Initiation

Before initiating TAVNEOS, consider performing the following evaluations:

- Liver Function Tests: Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS. TAVNEOS is not recommended for use in patients with cirrhosis, especially those with severe hepatic impairment (Child-Pugh C) *[see Warnings and Precautions (Full PI 5.1) and Use in Specific Populations (Full PI 8.7)]*.
- Hepatitis B (HBV) Serology: Screen patients for HBV infection by measuring HBsAg and anti-HBc. For patients with evidence of prior or current HBV infection, consult with a physician with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before or during treatment with TAVNEOS *[see Warnings and Precautions (Full PI 5.3)]*.

Recommended Dosage and Administration

The recommended dose of TAVNEOS is 30 mg (three 10 mg capsules) twice daily, with food.

Advise patients that TAVNEOS capsules should not be crushed, chewed or opened.

If a dose is missed, instruct the patient to wait until the usual scheduled time to take the next regular dose. Instruct the patient not to double the next dose.

Dosage Modifications Due to CYP3A4 Inhibitors

Reduce the dosage of TAVNEOS to 30 mg once daily when used concomitantly with strong CYP3A4 inhibitors.

CONTRAINDICATIONS

TAVNEOS is contraindicated in patients with serious hypersensitivity reactions to avacopan or to any of the excipients *[see Warnings and Precautions (Full PI 5.2)]*.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking TAVNEOS. During controlled trials, the TAVNEOS treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events *[see Adverse Reactions (Full PI 6.1)].*

Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS, every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.

If a patient receiving treatment with TAVNEOS presents with an elevation in ALT or AST to >3 times the upper limit of normal, evaluate promptly and consider pausing treatment as clinically indicated.

If AST or ALT is >5 times the upper limit of normal, or if a patient develops transaminases >3 times the upper limit of normal with elevation of bilirubin to >2 times the upper limit of normal, discontinue TAVNEOS until TAVNEOS-induced liver injury is ruled out *[see Adverse Reactions (Full PI 6.1)]*.

TAVNEOS is not recommended for patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risk and benefit before administering this drug to a patient with liver disease. Monitor patients closely for hepatic adverse reactions *[see Use in Specific Populations (Full PI 8.7)]*.

Hypersensitivity Reactions

TAVNEOS may cause angioedema *[see Adverse Reactions (Full PI 6.1)]*. In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization. If angioedema occurs, discontinue TAVNEOS immediately, provide appropriate therapy, and monitor for airway compromise. TAVNEOS must not be re-administered unless another cause has been established. Educate patients on recognizing the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program.

HBV reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg, in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Screen patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TAVNEOS. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TAVNEOS treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis, or HBV reactivation during and for six months following TAVNEOS therapy. In patients who develop reactivation of HBV while on TAVNEOS, immediately discontinue TAVNEOS and any concomitant therapy associated with HBV reactivation, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming TAVNEOS treatment in patients who develop HBV reactivation. Resumption of TAVNEOS treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Serious Infections

Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections.

Avoid use of TAVNEOS in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating TAVNEOS 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 TAVNEOS. Interrupt TAVNEOS if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with TAVNEOS 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 TAVNEOS should be interrupted if the patient is not responding to antimicrobial therapy. TAVNEOS may be resumed once the infection is controlled.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Hepatotoxicity *[see Warnings and Precautions (Full PI 5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (Full PI 5.2)]*
- Hepatitis B Virus (HBV) Reactivation *[see Warnings and Precautions (Full PI 5.3)]*
- Serious Infections *[see Warnings and Precautions (Full PI 5.4)]*

Clinical Trials Experience

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

The identification of potential adverse drug reactions was based on safety data from the phase 3 clinical trial in which 330 patients with ANCA-associated vasculitis were randomized 1:1 to either TAVNEOS or prednisone *[see Clinical Studies (Full PI 14)]*. The mean age of patients was 60.9 years (range of 13 to 88 years), with a predominance of men (56.4%) and Caucasians (84.2%). The cumulative exposure to TAVNEOS was 138.7 patient-years. Additionally, two phase 2 trials were conducted in ANCA-associated vasculitis. The cumulative clinical trial exposure from the phase 2 and 3 trials equals 212.3 patient-years.

The most frequent serious adverse reactions reported more frequently in patients treated with TAVNEOS than with prednisone were pneumonia (4.8% TAVNEOS vs. 3.7% prednisone), GPA (3.0% TAVNEOS vs. 0.6% prednisone), acute kidney injury (1.8% TAVNEOS vs. 0.6% prednisone), and urinary tract infection (1.8% TAVNEOS vs. 1.2% prednisone). Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and 2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the phase 2 trials.

In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzymes abnormalities. The most frequent adverse reaction that led to drug discontinuation reported by > 1 patient and more frequently reported in patients treated with TAVNEOS was hepatic function abnormal (1.8%).

The most common adverse reactions that occurred in ≥5% of patients and higher in the TAVNEOS group as compared with the prednisone group are listed in Table 1.

Table 1: Adverse Reactions Reported in ≥5% of Patients and Higher in TAVNEOS Group vs. Prednisone Group in Phase 3 Trial

Adverse Reaction	Prednisone (N=164) n (%)	TAVNEOS (N=166) n (%)
Nausea	34 (20.7)	39 (23.5)
Headache	23 (14.0)	34 (20.5)
Hypertension	29 (17.7)	30 (18.1)
Diarrhea	24 (14.6)	25 (15.1)
Vomiting	21 (12.8)	25 (15.1)
Rash	13 (7.9)	19 (11.4)
Fatigue	15 (9.1)	17 (10.2)
Upper abdominal pain	10 (6.1)	11 (6.6)
Dizziness	10 (6.1)	11 (6.6)
Blood creatinine increased	8 (4.9)	10 (6.0)
Paresthesia	7 (4.3)	9 (5.4)

N=number of patients randomized to treatment group in the Safety Population; n=number of patients in specified category.

Hepatotoxicity and Elevated Liver Function Tests

In the phase 3 trial, a total of 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the TAVNEOS group had hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. Study medication was paused or discontinued permanently due to hepatic-related adverse reactions in 5 patients (3.0%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. Serious hepatic-related adverse reactions were reported in 6 patients (3.7%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. A serious hepatic-related adverse reaction was reported in 1 patient in the TAVNEOS group in the phase 2 studies.

Angioedema

In the phase 3 trial, 2 patients (1.2%) in the TAVNEOS group had angioedema; one event was a serious adverse reaction requiring hospitalization.

Elevated Creatine Phosphokinase

In the phase 3 trial, 1 patient (0.6%) in the prednisone group and 6 patients (3.6%) in the TAVNEOS group had increased creatine phosphokinase. One TAVNEOS-treated patient discontinued treatment due to increased creatine phosphokinase.

DRUG INTERACTIONS

CYP3A4 Inducers

Avacopan exposure is decreased when co-administered with strong CYP3A4 enzyme inducers such as rifampin *[see Clinical Pharmacology (Full PI 12.3)]*. Avoid coadministration of strong and moderate CYP3A4 inducers with TAVNEOS.

CYP3A4 Inhibitors

Avacopan exposure is increased when co-administered with strong CYP3A4 enzyme inhibitors such as itraconazole *[see Clinical Pharmacology (Full PI 12.3)]*. Administer TAVNEOS 30 mg once daily when coadministered with strong CYP3A4 inhibitors.

CYP3A4 Substrates

Avacopan is a CYP3A4 inhibitor. Closely monitor patients for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with a narrow therapeutic window when coadministered with TAVNEOS *[see Clinical Pharmacology (Full PI 12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with TAVNEOS in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of avacopan to pregnant hamsters and rabbits during the period of organogenesis produced no evidence of fetal harm with exposures up to approximately 5 and 0.6 times, respectively, the exposure at the maximum recommended human dose (MRHD) of 30 mg twice daily (on an area under the curve [AUC] basis). Avacopan caused an increase in the number of abortions in rabbits at an exposure 0.6 times the MRHD *(see Animal Data)*. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study with pregnant hamsters dosed by the oral route during the period of organogenesis from gestation days 6 to 12, avacopan produced an increase in the incidence of a skeletal variation, described as supernumerary ribs, at an exposure that was 5 times the MRHD (on an AUC basis with a maternal oral dose of 1000 mg/kg/day). No structural abnormalities were noted with exposures up to 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

In an embryo-fetal development study with pregnant rabbits dosed by the oral route during the period of organogenesis from gestation days 6 to 18, avacopan caused an increase in the number of abortions at an exposure 0.6 times the MRHD (on an AUC basis with a maternal oral dose of 200 mg/kg/day), however, no evidence of fetal harm was observed with such exposures. Maternal toxicity, as evidenced by decreased body weight gains, was observed at exposures 0.6 times and higher than the MRHD (on an AUC basis with maternal oral doses of 30 mg/kg/day and higher).

In a prenatal and postnatal development study with pregnant hamsters dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, avacopan had no effects on the growth and development of offspring with exposures up to approximately 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

Lactation

Risk Summary

There are no available data on the effects of avacopan on the breastfed child or on milk production. It is unknown whether avacopan is secreted in human milk. Avacopan was detected in the plasma of undosed hamster pups nursing from drug-treated dams *(see Animal Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAVNEOS and any potential adverse effects on the breast-fed infant from TAVNEOS or from the underlying maternal condition.

Animal Data

Avacopan has not been measured in the milk of lactating animals; however, it was detected in the plasma of nursing offspring in a pre- and post-natal development study with hamsters at a pup to maternal plasma ratio of 0.37. This finding suggests that avacopan is secreted into the milk of lactating hamsters *[see Nonclinical Pharmacology (Full PI 13.1)]*.

Pediatric Use

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

Geriatric Use

Of the 86 geriatric patients who received TAVNEOS in the phase 3 randomized clinical trial for ANCA-associated vasculitis *[see Clinical Studies (Full PI 14)]*, 62 patients were between 65-74 years and 24 were 75 years or older. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

Patients With Renal Impairment

No dose adjustment is required for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (Full PI 12.3)]*. TAVNEOS has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

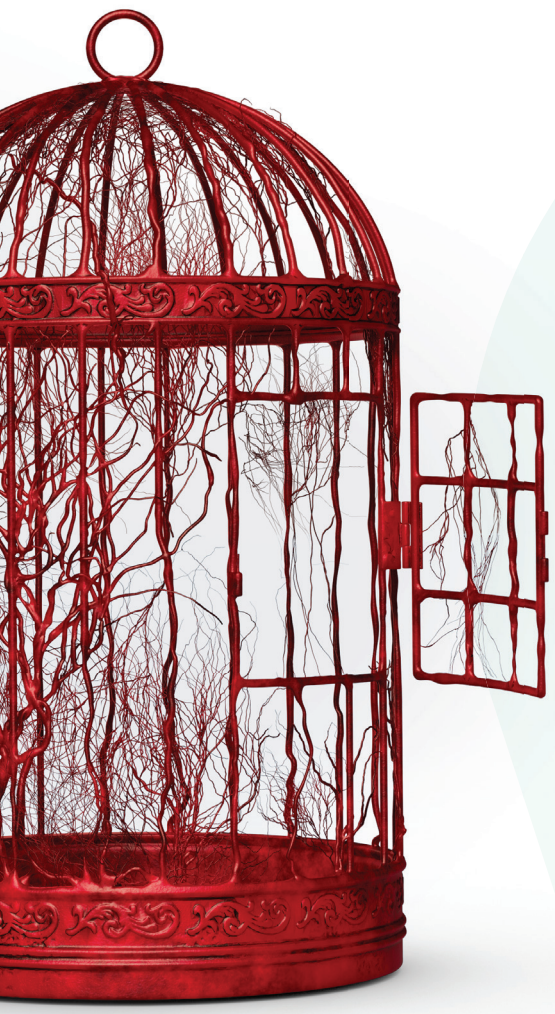
Patients With Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (as indicated by the Child-Pugh method) hepatic impairment *[see Clinical Pharmacology (Full PI 12.3)]*. TAVNEOS has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Based on Prescribing Information approved on 10/2021.

US-AVA-2100288 01/22

TAVNEOS®
(avacopan)



RELEASE

THE GRASP OF ANCA-ASSOCIATED VASCULITIS.

TAVNEOS® (avacopan) is a first-in-class, adjunctive treatment proven to help patients achieve and sustain remission.[1-4]

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Discover more about TAVNEOS by scanning the QR code or visiting **TAVNEOS.com/hcp**

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Serious hypersensitivity to avacopan or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Serious cases of hepatic injury have been observed in patients taking TAVNEOS, including life-threatening events. Obtain liver test panel before initiating TAVNEOS, every 4 weeks after start of therapy for 6 months and as clinically indicated thereafter. Monitor patients closely for hepatic adverse reactions, and consider pausing or discontinuing treatment as clinically indicated (refer to section 5.1 of the Prescribing Information). TAVNEOS is not recommended for patients with active, untreated, and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risks and benefits before administering this drug to a patient with liver disease.

Serious Hypersensitivity Reactions: Cases of angioedema occurred in a clinical trial, including 1 serious event requiring hospitalization. Discontinue immediately if angioedema occurs and manage accordingly. TAVNEOS must not be readministered unless another cause has been established.

Hepatitis B Virus (HBV) Reactivation: Hepatitis B reactivation, including life-threatening hepatitis B, was observed in the clinical program. Screen patients for HBV. For patients with evidence of prior infection, consult with physicians with expertise in HBV and monitor during TAVNEOS therapy and for 6 months following. If patients develop HBV reactivation, immediately discontinue TAVNEOS and concomitant therapies associated with HBV reactivation, and consult with experts before resuming.

Serious Infections: Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections. Avoid use of TAVNEOS in patients with active, serious infection, including localized infections. Consider the risks and benefits before initiating TAVNEOS in patients with chronic infection, at increased risk of infection, or who have been to places where certain infections are common.

ADVERSE REACTIONS

The most common adverse reactions (≥5% of patients and higher in the TAVNEOS group vs. prednisone group) were nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, and paresthesia.

DRUG INTERACTIONS

Avoid coadministration of TAVNEOS with strong and moderate CYP3A4 enzyme inducers. Reduce TAVNEOS dose when coadministered with strong CYP3A4 enzyme inhibitors to 30 mg once daily. Monitor for adverse reactions and consider dose reduction of certain sensitive CYP3A4 substrates.

TAVNEOS is available as a 10 mg capsule.

INDICATION

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

Please see the Brief Summary of the Full Prescribing Information for TAVNEOS on the previous pages.

To report a suspected adverse event, call 1-833-828-6367. You may report to the FDA directly by visiting www.fda.gov/medwatch or calling 1-800-332-1088.

References: 1. TAVNEOS® (avacopan) Prescribing Information. ChemoCentryx, Inc. **2.** Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med.* 2021;384(7):599-609. doi:10.1056/NEJMoa2023386 **3.** Khan MM, Molony DA. In ANCA-associated vasculitis, avacopan was superior to prednisone taper for sustained remission. *Ann Intern Med.* 2021;174(7):JC79. doi:10.7326/ACPJ202107200-079 **4.** U.S. Food and Drug Administration. Novel drug approvals for 2021. Published November 2021. Accessed November 4, 2021. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021

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