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THE Rheumatologist®

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

RHEUMINATIONS™

License to Cure

Greed, politics & medical licensure in the U.S.

■ BY PHILIP SEO, MD, MHS

William Osler, MD, had an idea.

Many institutions lay claim to the legacy of Osler, and by the time he arrived at Johns Hopkins Hospital in 1889 to become the first physician in chief of the institution, he was already widely acknowledged for his clinical acumen. He now wanted to spread that clinical acumen around.[1]

His idea was to bring medical trainees to the bedside.

To start, he thought that medical students, during their third and fourth years of medical training, should be assigned to *clinical clerkships*, in which they would gain direct experience working with patients. To his mind, however, this was not enough training to create a true physician. After graduating from medical school, physicians would spend several years living on hospital grounds to immerse themselves in the care of the infirm. These *residents* and medical students would join Dr. Osler as he personally examined each patient in the open ward. Because inpatients at Johns Hopkins Hospital were housed in an octagonal building, the patient beds were arrayed in a single room, like the spokes of a wheel. In the process of visiting each patient, medical personnel found themselves walking in a large circle as they

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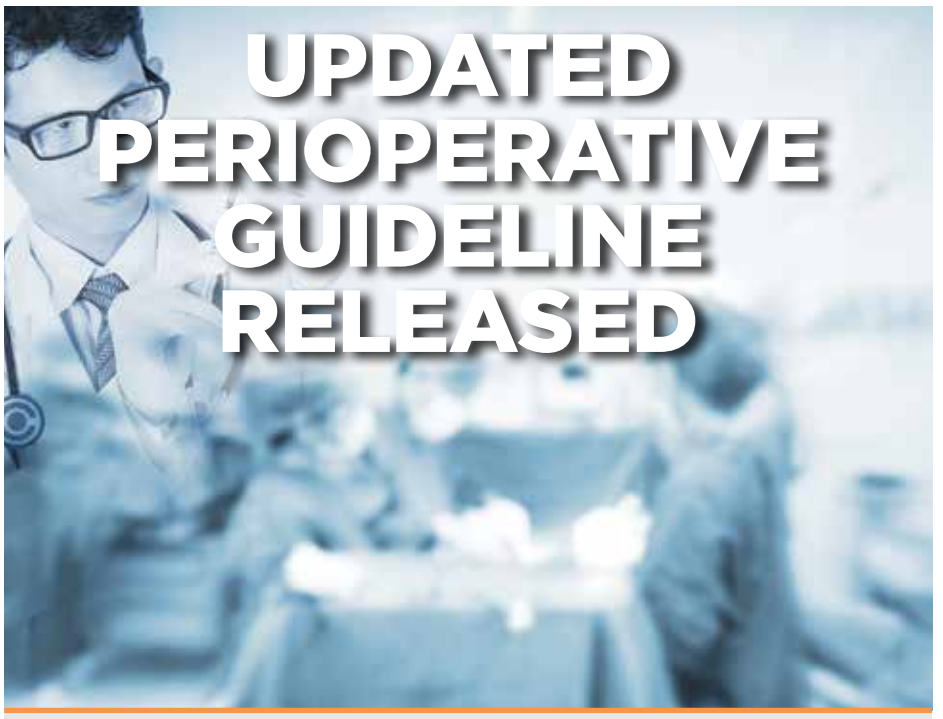

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RECOMMENDATIONS BALANCE RISKS OF INFECTION & DISEASE FLARE FOR PATIENTS UNDERGOING ELECTIVE TOTAL HIP OR TOTAL KNEE ARTHROPLASTY

■ BY RUTH JESSEN HICKMAN, MD

Due to immunosuppressive medications and other disease factors, patients with inflammatory arthritis or systemic lupus erythematosus (SLE) are at increased risk of infection following total hip arthroplasty (THA) or total knee arthroplasty (TKA). However, withholding such medications around the time of surgery increases the risk of disease flares. A new guideline update recently released by the ACR and the American Association of Hip and Knee Surgeons (AAHKS) provides clinicians with specific information to help with perioperative management (**https://www.rheumatology.org/Portals/0/Files/Perioperative-Management-Guideline.pdf**).[1]

DMARD Guidance

In 2017, the ACR and the AAHKS collaboratively produced the first guideline on perioperative management of these patients, specifically with respect to the use of disease-modifying anti-rheumatic drugs (DMARDs).[2] The recently released guideline update reflects changes in the medical literature since that time. It also provides specific recommendations on therapies newly approved by the U.S. Food

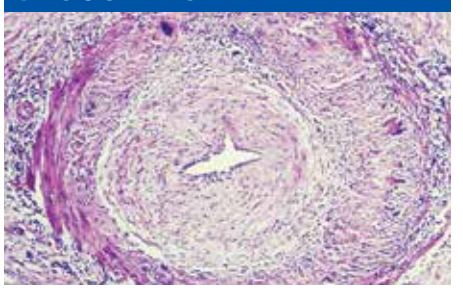
CONTINUED ON PAGE 9

RDAM

Rheumatic Disease Report Card 2022

■ PAGE 14

VASCULITIS



Giant Cell Arteritis

■ PAGE 36

IMAGE CASE

Milk of Urate Bulla

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INTERPROFESSIONAL

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AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

WILEY

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.

KRYSTEXXA® pegloticase

HORIZON

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.

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circumnavigated the perimeter of this octagonal building. Osler's staff, therefore, dubbed the activity *rounding*.[2]

This style of medical education has long been standard nationwide. In William Osler's time, however, the state of medical education was, quite frankly, a mess. First, no one could agree on what being a *doctor* actually meant. There were physicians like William Osler, who had trained in Europe and brought a European style of practice back to the States. Of course, this style included such practices as bloodletting, which would now be considered anathema. Because European medicine included treatments that could be worse than the diseases they purported to treat, two additional training systems had formed in the U.S.

Alternative Education

One school was founded by Samuel Thomson, a self-taught herbalist, who created a distinctly American approach to healthcare.[3] *Thomsonians* eschewed expensive European medicines in favor of natural approaches that purged patients of poisons by restoring the body's natural heat. The Thomsonian tradition gave rise to *eclectic medicine*, another distinctly American approach to healthcare that emphasized the use of herbs and physical therapy to pave the path to wellness.

Another school was founded by Samuel Hahnemann, who developed *homeopathy*, in which practitioners posit that small amounts of toxic substances can cure the diseases they would normally cause.[4] Evidence of the influence of homeopathy is the expression *hair of the dog that bit you*, which is now primarily used as an excuse to add a slug of whiskey to one's coffee the morning after a bender.

These schools flourished because of the needs of a growing nation. In Europe, physicians were the product of universities that had a reputation for training doctors and would vouch for their graduates' skills. At the time of this nation's founding, anyone who seemed to have the relevant skill set was welcome to refer to themselves as *doctor*. Most American physicians at the time could not afford to travel to Europe for medical training and, instead, were apprenticed to a more senior physician to learn the craft.[5] This homegrown system of training made Americans remarkably accepting of a wide range of medical philosophies among their physicians, even as medical training became formalized.

It should also be said that politics played a role in allowing these alternative schools to flourish. Andrew Jackson's presidency had left behind a populist, anti-elitist sentiment that found Thomsonian medicine particularly appealing.[6] The Jacksonians happily rejected expensive remedies in favor of *common sense cures* supported by alternative facts.

The other factor, of course, was greed. At some point, it became evident that money could be made in minting medical doctors, and diploma mills masquerading as medical schools sprung up across the country, like academic kudzu.[7]

The Flexnerian Revolution

In 1904, the American Medical Association (AMA) set out to reform American medical education. The AMA founded the Council on Medical Education (CME), which created the overall structure for a four-year medical education, comprising two years of anatomy and physiology, followed by two years of clinical work at a teaching hospital. The CME also set the minimum requirements for entry into medical school, thus introducing *pre-med* into the academic lexicon.[8]

Not surprisingly, these pronouncements made little impact. The public, in general, showed little interest in getting involved with telling schools how to train doctors. In the absence of a groundswell of moral outrage, little motivation existed for any medical school to come to heel.

Therefore, in 1908, the CME commissioned the Carnegie Foundation for the Advancement of Teaching to survey the current state of medical education in the U.S. The Carnegie Foundation, in turn, contracted the work to Abraham Flexner. Flexner was an interesting choice; he was an experienced educator, but had no training either in medicine or medical education.[9]

Flexner proceeded to visit each of the 155 medical schools that existed in North America at the time, each reflecting some mix of the extant medical philosophies. At the end of his travels, Flexner documented what he saw. The eponymous Flexner Report was scathing.

He found the vast majority of medical schools in the U.S. were not up to the task of educating doctors. In his report, he proposed five major reforms, based on the model created by William Osler at Johns Hopkins:[10]

1. Expand the prerequisites for medical training to include the basic sciences;
2. Revise classroom instruction to emphasize the application of the scientific method to the life sciences;
3. Provide access to medical wards, where students could learn, under supervision, from patients;
4. Create a full-time medical faculty dedicated to research and teaching; and
5. Strengthen state regulation of medical licensure.

If William Osler was the father of modern medicine, then Abraham Flexner was its midwife.[11] The impact of the Flexner Report on American medical education cannot be overstated. In the years following its publication, over half the medical schools in North America closed. The American Osteopathic Association introduced curricular changes in osteopathic medical schools that made the doctor of medicine (MD) and doctor of osteopathic medicine (DO) degrees nearly interchangeable. The Flexner Report struck the death knell for Thomsonianism and other forms of alternative medicine in U.S. medical schools.

The Flexner Report had a dark side that needs to be acknowledged. Underlying the report was the belief that society would be better off if only *the right people* became physicians. Only the well-off could afford to complete the prerequisites demanded by Flexner, followed by a doubling in the length of medical school education from two to four years. Similarly, only wealthy institutions had the resources to provide the type of education Flexner insisted was necessary. The Flexnerian model of medical education effectively prevented the *hoi polloi* from aspiring to become physicians.

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More importantly, Flexner was racist.[12] He asserted that Black physicians should only be allowed to treat Black patients. The Flexner Report led to the closing of five of the seven Black medical schools, leaving behind only Howard University College of Medicine and Meharry Medical College. Had those other schools remained open, an additional 35,000 Black physicians might have joined our ranks.[13]

Flexner & State Licensure

The lesser-discussed consequence of the Flexner Report was divorcing medical education from certification to practice. Prior to the Flexner Report, medical schools conferred both the medical degree and the right to practice medicine. Post-Flexner, medical schools provided only confirmation that a given student had completed an appropriate course of study to become a physician. The right to practice medicine was conferred by the state.[14]

From Flexner's point of view, this made perfect sense. At the time, the majority of medical schools were private institutions that were mainly interested in earning money. They were not a neutral or reliable arbiter of medical proficiency. Given that physician qualifications were a matter of public interest, the state seemed to be the natural guardian against quacks and charlatans.[15]

Although some states had introduced physician licensure previously, the Flexner Report made state licensure standard. Thus, in addition to reforms in medical education, the Flexner Report fueled the widespread adoption of a disjointed system in which each state sets its own standards for granting physicians a license to practice medicine.

Medical license reciprocity is the practice of granting physicians in one state the right to practice medicine in another state. You've never heard of this courtesy because, by and large, it doesn't exist—except in Michigan. The Michigan Board of Medicine will grant the right to practice to any physician who has had an active license for at least a decade anywhere in the U.S. or Canada.[16] Before the pandemic, no other state routinely granted this courtesy.

The New Mexico Medical Board allows *licensure by endorsement*, in which board-

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In addition to reforms in medical education, the Flexner Report fueled the widespread adoption of a disjointed system in which each state sets its own standards for granting physicians a license to practice medicine.

certified physicians who have been licensed and in practice in another state for at least three years can apply for a medical license without resubmitting proof of education or training.[17] *Endorsement* is not the same as *reciprocity*; it's just a shortcut. The candidate still needs to pay the licensure fee.

Now we come to the real reason that states have clung to this antiquated system of medical licensure. When you wonder why there is no national license to practice medicine, an obvious answer is profit.

The average cost of initial medical licensure for an MD in the U.S. (including a background check, where required) is $458. In five states, the cost of initial medical licensure is over $1,000; in 28 states, it is at least $500.[18] Nationwide, just granting medical licenses to physicians generates well over $200 million in total state revenue annually.

There is also a less obvious answer: competition. Controlling who can practice medicine allows the state to control competition. Physicians who live in a given state can be protected from having to compete with physicians from neighboring states. Because it is difficult for physicians to practice across state lines, a physician who earns money in a given state is more likely to spend (and pay taxes) on that money in that same state. State legislators have no particular incentive to increase competition for the physicians who voted them into office.

National Medical Licensure

Publicly, states aver that they continue to play a vital role in assuring the public that medical practitioners in their state are qualified to do so, as if physicians who see patients in Maryland might not be qualified to see patients in Delaware or Utah.

This ostensibly vital role played by state medical boards came into question during the past several years. At the height of the pandemic, when in-person visits were no longer feasible, many states loosened their licensure requirements to allow out-of-state physicians to provide remote care for patients through telemedicine. Unfortunately, these decisions were made on a state-by-state basis. And now that we have resigned ourselves to *the new normal*, licensure rules are being reinstated, even for telemedicine visits.

In his editorial in the *American Journal of Medicine*, Amr Sawalha, MD, director of the Division of Rheumatology at the University of Pittsburgh, argues:[19]

> *What is puzzling and defies logic, however, is that securing a license to practice medicine in one state does not allow for practicing the same type of medicine in another state in the same country. This contradicts the fact that accreditations and standards for medical education and training are regulated at the national level. Are patients living in this country different when they cross state lines? Does the human anatomy or physiology change when crossing the Mississippi River from Missouri to Illinois or driving across the George Washington Bridge from New York to New Jersey, for example? Does a physician really need four medical licenses from Arizona, Colorado, New Mexico and Utah to treat patients separated by the lines of the Four Corners Monument? Or is lupus (a disease I treat) different if a patient wakes up in an Eastern or a Western time zone?*

The groundwork to address this issue already exists, in the form of the Interstate Medical Licensure Compact (IMLC). The Compact extends the concept of *licensure by endorsement* to multiple states. A board-certified physician who holds an unrestricted medical license in a compact member state (and meets a number of prosaic requirements) is eligible for expedited licensure in other compact member states. At this time, only 10 states have made no moves toward joining the Compact.[20]

This is not a satisfactory solution. The Compact essentially is a paperwork work-around. Participants are still issued individual state licenses and are required to pay full licensure fees for each state, in addition to the $700 charged by the IMLC to facilitate the process. The IMLC does, however, demonstrate that a nationwide medical license using a single application is feasible.

State licensure of physicians was a natural outgrowth of the haphazard history of medical education in the U.S. Antebellum America was rife with physicians possessed of dubious qualifications, and there was no easy way for a prospective patient to differentiate a truly excellent physician from a physician who was, at best, ineffectual. Those days, however, are now safely behind us. The Oslerian model of medical education has been universal for some time; patients no longer risk encountering a Thomsonian or an herbalist at the local urgent care center. It is no longer reasonable to claim that a physician practicing in one state may not be competent to practice in another.

The current system of medical licensure impedes patient care. This impediment is particularly relevant in rheumatology, given the workforce shortages that plague our specialty. A nationwide medical license, along with judicious use of telemedicine, would dramatically increase patients' access to subspecialty care. William Osler himself practiced in Canada, Pennsylvania, Maryland and England. His peripatetic career demonstrates that a physician's skills are not limited by government borders.

State medical licensure was created to address a problem that no longer exists. We should now follow Osler's example and remove artificial impediments to clinical practice. **R**

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& Drug Administration (FDA) for these conditions (e.g., ixekizumab).

Post-surgery infections occur more often in patients with rheumatoid arthritis, spondyloarthritis and SLE than in patients with osteoarthritis, which is the most common reason for these replacements in the general population.[2] For example, one study found that patients with rheumatoid arthritis had twice the risk of developing an infection in the region surrounding their new prosthetic joint compared with patients with osteoarthritis.[3] The guideline recommendations are designed to balance the risks of post-surgical infection with the risks of disease flare, which can be quite serious in such conditions as severe SLE.

One of the guideline panel participants, Jasvinder A. Singh, MD, MPH, professor of medicine and epidemiology at the University of Alabama at Birmingham and a staff rheumatologist at the Birmingham Veterans Affairs Medical Center, notes these infections can range in severity from mild suture infections to deep infections that spread into the joint and prosthesis. "Although rare, the latter are disastrous—a huge deal for both the patient and the surgeon," he says.

Dr. Singh explains that recovery from such infections can require multiple surgeries over a one- to two-year period, causing major issues with patient disability and immobility, as well as a high risk of reinfection when a new prosthesis is eventually surgically implanted.

Susan M. Goodman, MD, professor of clinical medicine at Weill Cornell Medicine, an attending rheumatologist at the Hospital for Special Surgery, New York City, and the lead guideline author, notes that the patients who participated in the patient panel on the 2017 guideline were more concerned about infection risk than the risk of flare, even though disease flares after surgery may occur in more than half of patients.[1,2] "They were remarkably unified in their concern about infection," Dr. Goodman says. "They felt that while flares were very difficult, infections could become severe, and their unpredictable nature was even more difficult."

TKA and THA were originally selected as a focus for the perioperative guideline because they are performed so frequently, Dr. Goodman explains, adding, "They can provide the most data for us to work with in defining our recommendations." Although the guideline is intended to apply to patients undergoing these specific orthopedic surgery types, Dr. Singh notes that as a matter of practicality, some clinicians may extrapolate from them to use in other surgical settings (e.g., shoulder replacement) for which guidelines do not currently exist.

Guideline Development

The rheumatologists, orthopedic surgeons and infectious disease specialists who updated this current guideline performed additional systematic literature review and wrote population, intervention, comparator and outcome (PICO) questions to reflect current medications. Like other recent ACR guidelines, they also used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the evidence and the strength of the recommendations using group consensus. Dr. Singh notes that this was a highly collaborative process, with each group contributing their expertise; consensus for the recommendations was quite high, with none achieving less than 80% agreement.

No new randomized, controlled trials informed the evidence base for this update. Dr. Goodman points out that the literature used to make these recommendations contained very little data directly comparing outcomes in patients taking or withholding anti-rheumatic medications at the time of surgery. "Therefore, we applied studies that determined the risk of infection with the medications in patients who were not undergoing surgery and used that to assess risk," she explains. Some data were also extrapolated from patients without rheumatic diseases. Clinicians can make their own assessment of the data used to compile the guidelines via information freely available from the ACR: **https://www.rheumatology.org/Portals/0/Files/Perioperative-Management-Guideline-Appendix-5.pdf**.

Recommendations

A brief discussion of some of the recommendations from the guideline follows. For the full set of recommendations and their context, please see the complete guideline. The recommendations apply to patients with inflammatory arthritis (i.e., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or juvenile idiopathic arthritis) and patients with SLE who are undergoing elective THA or TKA. All these recommendations are conditional, indicating the level of evidence on which they are based is low or that the decision may be subject to patient preference.

Recommendation: *For patients with inflammatory arthritis or SLE, the following DMARDs should be continued through surgery without interruption: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and apremilast.*

The existing literature suggests these drugs may be taken safely during the perioperative period. Observational studies have found no increased risk of infections in patients taking these drugs. This recommendation is unchanged from the previous guideline, but also includes the addition of the synthetic DMARD apremilast.

Recommendation: *For patients with non-severe SLE, most medications should be withheld one week prior to surgery (except those listed directly above).*

This recommendation, unchanged from the previous guideline, includes such medications as mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus.

Recommendation: *For patients with inflammatory arthritis, withhold all biologics prior to surgery and plan the surgery shortly after the next dose would be due.*

This time frame was picked because drug levels and drug biological activity are low during this time, which help maximize safety, Dr. Singh explains. For example, for a patient taking adalimumab, normally dosed every two weeks, surgery could be planned for week 3 after the last given dose; similarly, for rituximab, normally dosed every six months, surgery could be planned for month 7 after the last given dose. This recommendation also applies to the recently introduced biologics ixekizumab, a blocker of interleukin 17, and guselkumab, a blocker of interleukin 23.

Recommendation: *For patients with inflammatory arthritis or SLE who had anti-rheumatic therapy withheld prior to surgery, restart therapy once the wound shows evidence of healing without any signs of infection.*

Typically, this occurs about 14 days after surgery, but it might be earlier or later, depending on the status of the wound and the patient's overall health. Dr. Singh explains, "You end up skipping a dose. You maximize safety, but you don't risk flare by holding it for too long."

Recommendation: *For patients with inflammatory arthritis, hold Janus kinase (JAK) inhibitors for at least three days prior to surgery.*

This recommendation, which applies to the targeted synthetic DMARDs tofacitinib, baricitinib and upadacitinib, was changed from a seven-day hold in the previous guideline. Dr. Singh notes that since that time, we've gained a better understanding of the clinical effects of these drugs, suggesting a more rapid reversal of immunosuppressive effects than previously believed. This makes it safer to withhold them for a shorter period.

Recommendation: *For patients with severe SLE, continue the usual dose of the following drugs through surgery: mycophenolate mofetil, mycophenolic acid, azathioprine, mizoribine* [editor's note: not available in the U.S.], *cyclosporine, tacrolimus, anifrolumab, voclosporin, belimumab and rituximab.*

Dr. Singh points out that in severe lupus, the risk of organ failure and severe outcomes from uncontrolled disease is far worse than any risks from the drug being continued. "Some of those mortality and organ failure risks do go up just because of fluid shifts and stress from the surgery itself," he adds, "so it's quite critical to continue medications in those instances." Voclosporin and anifrolumab, two new drugs for lupus, were added to this list in the updated guideline; however, we don't currently have specific data relevant to their use in the perioperative period.

Given its six-month dosing interval and its known risk of severe infection, perioperative management of rituximab has long been a challenge. Although not technically approved for SLE by the FDA, it has increasingly been used in this context. In contrast to the previous guideline, this update separates the use of rituximab in SLE from its use in other diseases (e.g., to be held in inflammatory arthritis). For *non-severe* SLE, surgery should be performed in the month after the last expected dose (i.e., month 7); in *severe* SLE, surgery should be performed in the last month of

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Post-surgery infections occur more often in patients with rheumatoid arthritis, spondyloarthritis & SLE than in patients with osteoarthritis.

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the dosing cycle (i.e., month 6) to minimize infection risk while not skipping a dose.

Recommendation: *For patients with inflammatory arthritis or SLE who are taking baseline glucocorticoids, continue this daily dose but do not administer additional glucocorticoids on the day of surgery.*

This recommendation is unchanged from the previous guideline, but two new sources support it. Dr. Goodman explains that administering additional glucocorticoids on the day of surgery became commonplace after reports of severe hypotension and death in a patient who had stopped glucocorticoids several days prior to surgery. "More recently, no differences in hemodynamics have been seen when patients receive their usual dose, so that is our current recommendation," she adds.

Putting Recommendations in Context

As always, these recommendations only provide guidance; physicians must use their own clinical judgment in combination with patient input to make decisions. For example, in a patient whose disease has been historically difficult to control, the best choice may be continuing to take a DMARD, even if a conditional recommendation in the guideline suggests holding it.

Similarly, it may make sense for some patients to temporarily hold a medication, even when conditional guidance would be to continue it. For example, this might be the case for a patient with a history of severe infections or a previous joint infection, or a patient whose disease has been very stable and not subject to flares. Dr. Singh points out that this conversation between the patient, the orthopedic surgeon and the rheumatologist is critical, so that each patient's individual risk can be fully considered.

Building the Evidence Base

The updated guideline does not provide information with respect to patients on multiple therapies. Dr. Singh explains that little to no evidence currently exists about how to handle DMARD combination therapy in the perioperative period. We also don't have much information about the benefits of holding one vs. two doses of these drugs.

One research challenge, Dr. Singh points out, is that the baseline risk of these infections is low, so it can take very large study sizes to see differences in rates of infection or other complications. He would also like to see prospective studies of rates of flares in these patients, in addition to the current retrospective data. "We have unanswered questions in almost every sphere of the guideline; we would ideally want high quality randomized trials in several of these conditions for almost every medication," he adds. R

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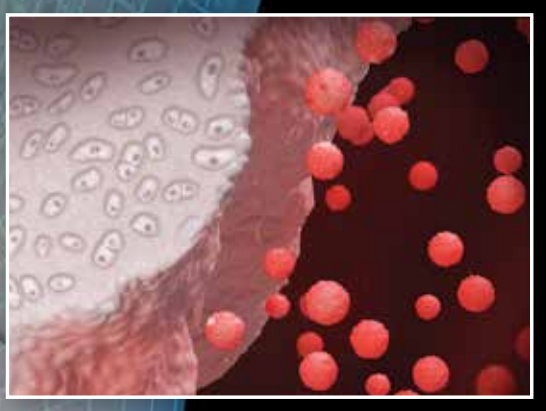

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- **Non–cross-linked sodium hyaluronate derived from bacterial fermentation**
- **Stable molecular weight of 2.5 million da**
- **SynoJoynt treatment is covered by Medicare and most insurance plans; assistance available through the Arthrex Reimbursement Support Program**

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INDICATIONS

SynoJoynt treatment is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (eg, acetaminophen).

CONTRAINDICATIONS

Do not use SynoJoynt treatment to treat patients who have a known hypersensitivity to hyaluronan preparations.

Do not use to treat patients with knee joint infections or to treat patients with infections or skin disease in the area of the injection site.

WARNINGS

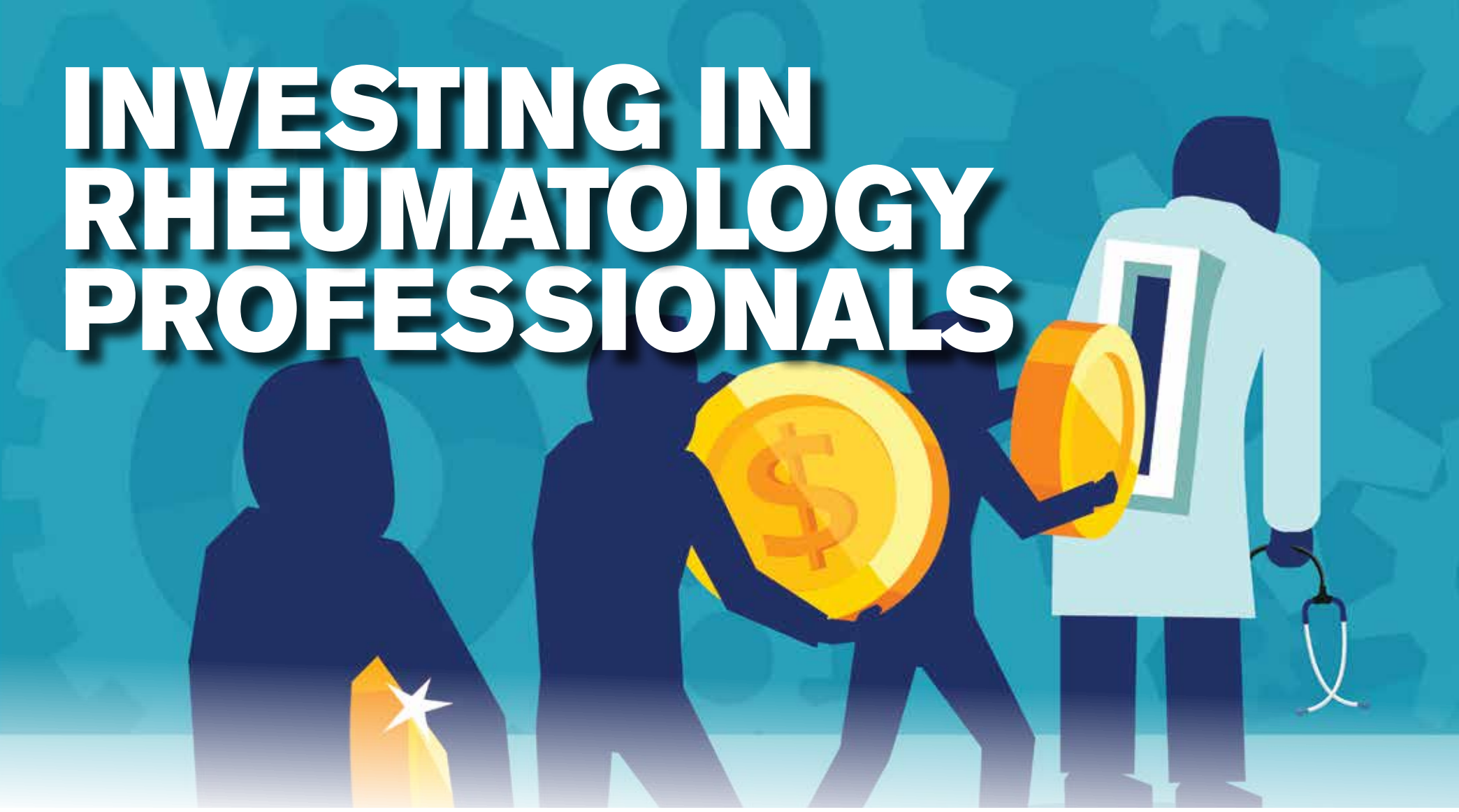
Do not concomitantly use disinfectants containing quaternary ammonium salts or chlorhexidine for skin preparations because hyaluronan can precipitate in their presence.

Do not inject intravascularly because intravascular injections of SynoJoynt treatment may cause systemic adverse events.

Contact an Arthrex representative to trial SynoJoynt injections

Arthrex®

INVESTING IN RHEUMATOLOGY PROFESSIONALS



The Rheumatology Research Foundation supports ARP members with research & training awards

BY KATIE ROBINSON

In fiscal year 2022, the Foundation committed approximately $1.43 million to ARP members, representing a 160% increase over the previous fiscal year.

In Brief

The Rheumatology Research Foundation supports ARP members who seek to improve the health of patients living with rheumatic disease.

The mission of the Rheumatology Research Foundation, a division of the ACR, is to advance research and training to improve the health of patients living with rheumatic disease. It supports career advancement, mentorship, professional development and education of professionals working in the disciplines essential to these patients.[1]

"The Foundation understands that the support of Association of Rheumatology Professionals (ARP) members is important to achieving its overarching mission because these health professionals work in so many of the disciplines—occupational therapy, physical therapy (PT), pharmacy, practice management, etc.—that are essential to improving the health of patients living with rheumatic disease," says Heather Benham, DNP, APRN, CPNP-PC, who works in pediatric rheumatology at Scottish Rite for Children, Dallas, and is a member of the Foundation's Impact Advisory Council. "ARP members can already take advantage of the many funding opportunities offered by the Foundation."

Awards

Since 1985, the Foundation has committed more than $205 million to the field of rheumatology through more than 4,115 research and training awards. In the current fiscal year, the Foundation will commit around $12.84 million to fund more than 120 awards for education, training, career development and research. Around a quarter of these awards will support efforts to recruit and train the next generation of rheumatology professionals; the remaining funds will be awarded to advance research projects leading to innovations in treating patients with rheumatic diseases and to supporting the early career development of rheumatology researchers.[2]

In fiscal year 2022, the Foundation committed approximately $1.43 million to ARP members, representing a 160% increase over the previous fiscal year. "Because we have so many deadlines throughout the year, we are unsure what the total allocated to ARP members will be this year, but we remain dedicated to funding as many projects as possible," says Eryn Marchiolo, MPH, vice president of mission at the Foundation.

By assisting with large and small sum grants, the Foundation supports career advancement, mentorship, professional development and education of ARP members in the specialty of rheumatology, says ARP President Barbara Slusher, MSW, PA-C, supervisor of advanced practice providers at MD Anderson Cancer Center in Galveston and League City, Texas.

"The Foundation offers short-term mentoring and career advancement in the form of four- to eight-week awards for preceptorships for medical and graduate students who are interested in exploring the field of rheumatology. These awards offer a unique opportunity for trainees to work closely with an ACR/ARP rheumatology mentor to learn more about the field of rheumatology," says Ms. Slusher. "For longer-term mentorship and career advancement, the Foundation offers the two-year Future Physician Scientist Award, for MD/PhD or DO/PhD candidates, and the three-year Scientist Development Award for rheumatologists and rheumatology professionals to pursue innovative research ideas."

For health professionals new to rheumatology, the Health Professional Online Education Grant provides financial support to complete the ARP's flagship courses: Fundamentals of Rheumatology and eBytes. This grant can also be used by health professionals, including doctors of pharmacy, nurse practitioners, physician assistants and fellows looking for more in-depth education, such as the Advanced Rheumatology Course, explains Ms. Slusher.

Workforce Expansion

According to Dr. Benham, "One of the Foundation's most recent funding programs, the Mentored Nurse Practitioner/Physician Assistant Award for Workforce Expansion, has been important in addressing the current workforce shortage facing the subspecialty of rheumatology."

The Mentored Nurse Practitioner/Physician Assistant Award for Workforce Expansion is a 12-month mentorship between nurse practitioners and physician assistants and an ACR member rheumatologist. The award provides resources and the framework of knowledge and skills needed by nurse practitioners and physi-

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cian assistants who are new to rheumatology to facilitate their integration into a rheumatology practice. The maximum award amount is $25,000 and the application deadline is Dec. 1.[3]

"The Mentored Nurse Practitioner/Physician Assistant Award for Workforce Expansion seeks to help increase the supply of rheumatology healthcare professionals, especially in underserved areas. Since the inception of this funding opportunity in 2019, the Foundation has awarded funds to 37 programs," says Dr. Benham. "Our pediatric rheumatology center was one of the initial awardees and this allowed us to add another nurse practitioner to our care team, something that has benefited our patients and families in an immense way."

Ms. Marchiolo says the Foundation continues "to want to grow the Mentored Nurse Practitioner/Physician Assistant Award for Workforce Expansion. We have seen really great outcomes over the first cycles of the award and would love to see an increase in applications."

Research Projects

ARP members benefit from the Foundation's financial support for educational offerings as well as from the opportunity to submit research proposals for funding, says Linda S. Ehrlich-Jones, PhD, RN, associate director at the Center for Rehabilitation Outcomes Research at Shirley Ryan AbilityLab, Chicago, and a member of the Foundation's Development Advisory Council.

Dr. Ehrlich-Jones explains that along with the Scientist Development Award, research awards include Career Development Bridge Funding (R Bridge); Career Development Bridge Funding (K Supplement and K Bridge); and the Investigator Award. In addition to the Mentored Nurse Practitioner/Physician Assistant Award for Workforce Expansion, education awards include the Clinician Scholar Educator Award and the Lawren H. Daltroy Preceptorship in Health Communication.

Further, the Innovative Research Award provides funding to independent researchers to pursue ideas that could lead to breakthroughs in discovering new treatments for patients with rheumatologic diseases, improve patient outcomes and/or increase quality of care. The award provides support for studies focused on generating new insights into the cause, progression, treatment and outcomes of rheumatic and musculoskeletal diseases. The two-year award offers up to $400,000 ($200,000 per year). The next award term starts in July 2023.[4]

Recent Innovative Research Award recipients and ARP members include Daniel White, PT, ScD, MSc, an associate professor in the Department of Physical Therapy, University of Delaware, Newark, and Susan Murphy, ScD, OTR, an associate professor in the Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor.

"Our group felt the need to study telehealth for knee osteoarthritis given the COVID-19 pandemic and the closing of PT outpatient clinics, leaving patients without treatment options. As well, there is a major need to improve access to PT for all," says Dr. White. "We are using the award to conduct a randomized trial to investigate if telehealth physical therapy can improve physical activity, function and pain in adults with knee osteoarthritis compared [with] usual care. … To date, we have recruited and randomized over 70% of our sample, who come from over 35 different states, and include 20% of people who are from underrepresented minority groups."

Dr. Murphy explains that she received the Innovative Research Award with co-principal investigator Dinesh Khanna, MBBS, MSc, professor of rheumatology at Michigan Medicine and director of the University of Michigan's scleroderma program, to conduct a clinical trial to test a resilience-based energy management program, called RENEW, for people with systemic sclerosis.

"In this project, we are examining whether the RENEW program has effects on fatigue and other symptoms, like pain interference and depressed mood. The program has online and app-based learning modules from established cognitive behavioral therapy treatments and positive psychology theory to address different health behaviors, and we have trained patient partners who also have systemic sclerosis to serve as health coaches in the program," Dr. Murphy says. "The clinical trial is going very well. We have about 100 people enrolled so far, with a goal of 168 participants. Because all study procedures are remote, we have participants from seven countries in the world taking part."

Looking Ahead

Dr. Benham notes that as ACR Convergence 2022 will be in person again, the Student and Resident ACR Convergence Scholarship will cover registration fees and $2,000 for travel expenses, plus a one-year ACR/ARP membership for students interested in a career in rheumatology. As a part of the Foundation's Choose Rheumatology campaign, the award aims to introduce students and residents in areas of the U.S. underserved by rheumatologists and rheumatology professionals to the specialty of rheumatology. Students and residents from racial and ethnic groups who are underrepresented in health-related science are also eligible to receive the award. At the meeting, which runs Nov. 10–14 in Philadelphia, awardees will attend a Choose Rheumatology event.[5,6]

Looking ahead, the ARP is assisting in evaluating the Foundation's portfolio to identify any gaps in support, as well as looking at potential new opportunities for grant support of health professionals.

"We are excited that we have three ARP members on the Portfolio Review Panel this year, which is an increase over the previous panel," says Ms. Marchiolo. "It is a process that we go through every five years; we conduct a thorough review of the efficacy of the Foundation's awards programs and identify gaps and future needs." The panel will make recommendations for necessary program changes to better meet the needs of the rheumatology community to the Foundation's board in February 2023.

The "ARP is grateful for the ongoing efforts by the Foundation in support of our varied membership. We believe that, together, we are a powerful force to invite, recruit, develop, educate and ultimately retain health professionals dedicated to a career in rheumatology," Ms. Slusher notes.

Dr. Benham says that some ARP members may be unaware of what the Foundation has to offer. "As an ARP member, I look to the Foundation as a resource for research and educational support. I think an important aspect moving forward is to connect ARP awardees with other ARP members to provide mentorship and guidance."

Dr. Ehrlich-Jones suggests that, along with looking for mechanisms to support clinical and research efforts, "I believe that ARP members look to the Foundation as a source of help for their patients. Through the support from the Foundation, patients will reap the benefits of the research that can help improve the quality of their lives." R

Katie Robinson is a medical writer based in New York.

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RHEUMATIC DISEASE REPORT CARD 2022

More work needed by many states to improve care for patients with rheumatic diseases

BY VANESSA CACERES

In honor of Rheumatic Disease Awareness Month, the ACR released a new Rheumatic Disease Report Card as part of its Simple Tasks public awareness campaign. The report card seeks to help answer the question, "How easy is it to live with rheumatic disease in my state?" (See **https://simpletasks.org/reportcard**.)

First released in 2018, the report card has been updated to provide new scores to see how much states have improved. It considers such factors as access to care, affordability, and activity and lifestyle elements when providing each state with a score and corresponding letter grade.

The *access* category considers number of residents per rheumatologist, the percentage of residents who lack insurance coverage, the strength of the state's laws to limit prior authorization and the strength of the state's legislation to limit insurers' use of step therapy.

The *affordability* category awards states points on the basis of the presence of state legislation limiting insurer use of specialty tiers, the strength of the state's laws promoting pharmacy benefit manager (PBM) transparency and the presence of state legislation preventing insurers from implementing copay accumulators.

The *activity* category looks at such factors as the prevalence of arthritis-attributable activity limitation among adults, the percentage of adults who are physically inactive and the prevalence of Centers for Disease Control and Prevention (CDC) funded arthritis intervention programs.

Each state received a numerical score and a letter grade in each area. The total potential score was 150 points. States then received an overall letter grade to reflect their score.

Which States Made the Grade?

No states received an overall grade of A. However, five states achieved a B, the highest grades awarded:

- New York (a score of 111 out of 150);
- Virginia (106/150);
- Maryland (105/150);
- California (93/150); and
- Illinois (92/150).

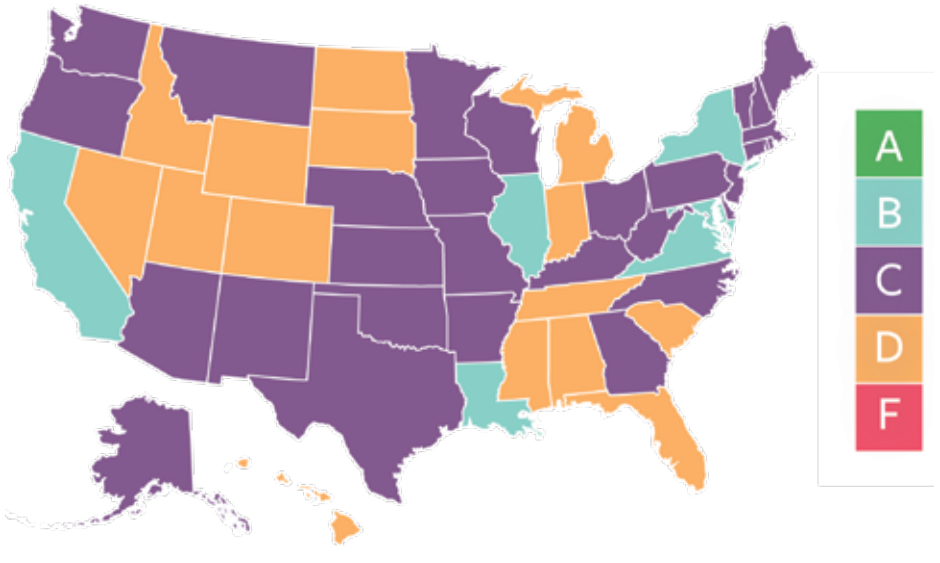
Most states received an overall grade of C or D (see Figure 1, below).

Maryland had the highest score in the 2018 report card, followed by New York, Vermont, Colorado and Connecticut.

This year's top scorer, New York, earned an A for access and was the only state to do so in that category. "The A in the access category was due to the strength of its state legislation to limit insurer use of prior authorization and step therapy, as well as its low ratio of people per rheumatologist," says Jocelyn Givens, director of public relations and communications at the ACR.

New York received a B for affordability and activity.

FIGURE 1



The states that received the lowest scores were Idaho (42/150), Mississippi (39/150), South Carolina and Nevada (both 38/150) and Wyoming (37/150). All five earned an overall letter grade of D.

South Carolina, Wyoming and Mississippi were among the lowest in the 2018 report card, along with Alabama and Oklahoma.

This year's report card recognizes Oklahoma as the most improved state, moving to an overall C grade vs. a D in 2018. Its score went up by 31 points, and it moved from the lowest scoring state to a ranking of 20th place in 2022. Oklahoma is one of only 13 states that have passed laws to ban state-regulated insurance plans from using copay accumulators. These accumulators are used by insurers and PBMs to prevent drug manufacturer copay assistance coupons from counting toward a patient's deductible and maximum out-of-pocket spending.

Oklahoma and Louisiana were the only two states to see an increase in their grades.

This year's lowest ranking state, Wyoming, had an F for both access and affordability, and a C for activity. The state can improve these areas by passing legislation that promotes PBM transparency and preventing insurers from implementing step therapy, prior authorization, copay accumulators and specialty tiers, Ms. Givens says.

Access, Affordability, Activity

Looking further at grades given by category, states are a mixed bag in terms of access. While New York received an A, most other states earned a B, C, or D. South Carolina, Nevada, Utah and Wyoming all earned an F for access.

The report card points out the stark difference in some states regarding the number of rheumatologists working there. In Massachusetts, there is one rheumatologist for every 19,000 people; in Wyoming, it's one rheumatologist per 156,611 people. The overall average is one rheumatologist per 40,000 people, according to the report. A lack of health insurance also remains a problem for many with rheumatic diseases.

Under affordability, many states received a D or F—in fact, 20 states received an F. This is often due to "exorbitantly expensive" prescribed treatment costs. Although some states have made changes to reform PBM practices since 2018, fewer than half have put limits on insurers' use of specialty tiers or prohibited the use of copay accumulator programs that leave patients with higher out-of-pocket costs. Louisiana received the only A for affordability. A handful of other states received a B.

States fared better overall in the activity category, with more receiving an A or B. Mississippi was the one state to receive an F.

All states and the District of Columbia now have at least one CDC-funded activity program implemented by the YMCA or other prominent group.

Policymakers can help find funding for evidence-based rheumatology intervention programs, such as those funded by the CDC, and support program participation in rural areas and underserved communities, according to the report.

Using the Report Card Results

Policymakers, rheumatology professionals and patients can work together and use the report card findings to address access, affordability and lifestyle factors to improve the lives of those limited by pain and disability, Ms. Givens says. This is important because of the large number of people living with chronic diseases, such as rheumatoid arthritis and lupus, who are finding it harder to afford their prescription medicines and access specialized care, she adds.

The ACR has continued to lobby at both the federal and state level for improvement in the areas of access, affordability and activity, as outlined in the report. Leaders have seen some progress in the past four years.

"The full report card gives all the states scores in individual categories, as well as case studies on key issues impacting the scores and an appendix that provides all the data on how the scores were compiled," Ms. Givens says. "We hope states will use this information to identify the various opportunities they have to raise their score."

With the majority of states receiving an overall grade of C, there is still a lot of work to be done to help those living with rheumatic disease, she adds. **R**

Vanessa Caceres is a medical writer in Bradenton, Fla.

New Law Puts Scrutiny on PBM Practices in Florida

Pharmacy benefit managers under a microscope once again

■ BY CATHERINE KOLONKO

Florida lawmakers joined efforts in other states this year to curb questionable pricing practices of pharmacy benefit managers (PBMs), the increasingly controversial financial intermediaries between drug makers and drug takers.

Health insurance companies hire PBMs to negotiate discounts and rebates with drug companies to lower prescription drug costs for their members. However, suspicion over who really benefits has led to calls for legislative action at both the state and federal levels.

Proponents of PBMs maintain they help lower the cost of prescription drugs and are an important player in the healthcare industry. Nevertheless, a 2020 Supreme Court ruling that gave states the right to regulate them may prompt greater examination of how they operate.

Recently, Florida legislators passed into law HB 357, which includes a $10,000 fine for PBMs that don't register with the state Office of Insurance Regulation (OIR).[1] The law changed enforcement responsibility from the Florida Board of Pharmacy to the OIR, giving more teeth to the registration requirement, as well as protection for pharmacies when audited by a PBM or health plan.

"This bill is a step forward on PBM regulation and is especially beneficial for independent pharmacists," says Robert Levin, MD, FACR, president of Alliance for Transparent and Affordable Prescriptions and past president of the Florida Society of Rheumatology. "The enforcement of registration with the OIR is a good thing as well.

"There is much more work to be done to benefit patient access, which was not included in this legislation," Dr. Levin added in an email interview.

PBM Pricing Influence

Four years ago, the Florida Legislature banned gag clauses, meaning PBMs could no longer contractually forbid pharmacies from telling patients when a cash payment for a prescription is cheaper than their insurance copayment.[2] Similar bans have passed at the federal level.

Other provisions of Florida's new law apply mostly to pharmacy audits that won't directly impact rheumatologists and their patients, says Joseph Cantrell, JD, ACR senior manager of state affairs. He views the law as a positive development, but says more reform is needed to achieve greater transparency and reduce the drug pricing power of PBMs.

"I don't want to undersell an improvement, but $10,000 isn't even pocket change for PBMs," Mr. Cantrell notes.

In the U.S., 66 PBMs manage the pharmacy benefits of about 270 million Americans, according to the National Association of Insurance Commissioners. Three of the largest of these companies—Express Scripts, CVS Caremark and OptumRx—hold a combined market share of almost 90%.[3]

Large PBMs increase their influence in the marketplace by taking rebates from drug companies eager to get their medications listed in prime position on health plan formularies. Despite calls for transparency in the public interest, companies generally keep negotiation details confidential, citing intellectual property protections.

It's questionable whether those rebates ultimately lower prices for the patient at the pharmacy counter, notes Mr. Cantrell. Instead, it is suspected that rebate funds often get reclassified as income or administrative fees and added to the PBM revenue stream. The rebates "often don't flow back to their intended source, which is supposed to be the patient and the health plan," says Mr. Cantrell.

Pricing Practices

Patient advocates and lawmakers grappling with increasing costs of prescription drugs point to a highly controversial practice known as spread pricing. The term describes how a PBM may boost profits by charging health plans and payers more for a drug than the pharmacy reimbursement amount and pocketing the difference.

In Florida, additional scrutiny of PBM pricing practices could result from an executive order handed down by Gov. Ron DeSantis in July soon after he signed HB 357 into law. The order requires Florida state agencies to audit PBM contracts entered into with state Medicaid plans to ensure that costs to the state are justified.[4]

The governor's order calls for state agencies to prohibit spread pricing and financial clawbacks in future contracts with PBMs. It also directs them to capture data on rebates and payments from drug companies, insurers and pharmacies.[4]

Clawback is a practice in which a PBM claws back the difference between what the prescription cost the pharmacy and the insurance copayment amount. Not only is it like penalizing someone for having health insurance, it's also unclear if that fee gets returned to the health plan in the form of lower costs, according to a 2018 article from *Kaiser Health News*.[5]

The executive order to capture data on rebates is in line with patient advocacy efforts to make information public about how drug companies use them to gain PBM formulary placement and market access, says Dr. Levin.

continued on page 21

Updated Guideline Introduces Recommendations for Prevention & Treatment of Glucocorticoid-Induced Osteoporosis

■ FROM THE COLLEGE

PANCHENKO VLADIMIR / SHUTTERSTOCK.COM

ATLANTA—The ACR released a summary of its updated guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in September. Many patients take glucocorticoids for a variety of inflammatory conditions, and anyone who is taking glucocorticoid medications and has other risk factors for osteoporosis increases their risk of developing glucocorticoid-induced osteoporosis. New osteoporosis medications and new literature have become available since the last ACR treatment guideline was published in 2017.

"One major side effect of glucocorticoid therapy is bone loss and an increase in the risk of fractures. Fractures can cause significant morbidity and be associated with an increased risk of mortality," said Mary Beth Humphrey, MD, PhD, co-principal investigator of the guideline and interim vice president for research and a professor of medicine at the University of Oklahoma Health Sciences Center. "With newly approved osteoporosis medications and a review of the relevant literature, we felt it was important to update the guideline."

The guideline team conducted an updated systematic literature review for clinical questions on non-pharmacologic and pharmacologic treatment addressed in the 2017 guideline, and for questions on new pharmacologic treatments, discontinuation of medications, sequential and combination therapy. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the certainty of evidence. A voting panel including clinicians and patients achieved ≥70% consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

The guideline includes recommendations on abaloparatide and romosozumab, which are two medications that are newly available since the 2017 guideline, as well as recommendations for other osteoporosis medications.

The guideline also recommends sequential therapy (any treatment regimen in which the patient is given one treatment followed by another), which was not addressed in the previous guideline. The recommendations for sequential therapies are based in part on some study designs, long-term follow-up studies, and new clinical trials.

"Some physicians may be surprised about the need for sequential therapy when completing a course of denosumab, parathyroid hormone/parathyroid hormone related protein, or romosozumab. If not done, patients could be at risk of rapidly developing vertebral fractures and bone loss," said Linda Russell, MD, director of perioperative medicine, director of the Osteoporosis and Metabolic Bone Health Center for the Hospital for Special Surgery and co-principal investigator of the guideline.

The updated guideline also gives more flexibility on drug selection and considers patient and physician preferences.

"The previous guideline rank-ordered medication for the treatment of glucocorticoid induced osteoporosis. We felt it was important that this guideline reflect patient/physician decision making," said Dr. Humphrey.

A full manuscript has been submitted for journal peer review and is anticipated to be published in rheumatology journals in early 2023. The summary of the guideline recommendations can be viewed in full on the ACR website: **https://tinyurl.com/32vbw225**. R

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-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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"Our advocacy organizations have been pushing for rebate transparency," says Dr. Levin. "While this will not affect commercial insurance plans regulated by the state, it is an excellent start."

Lasting Effects?

For those wondering if the recent spotlight in Florida on PBM pricing practices and calls for greater industry transparency signals a turning point for Florida healthcare policymakers, Mr. Cantrell cautions, "not so fast."

He sees recent actions more as a step in the right direction than any sort of sea change, adding that it's no time to slack off advocating for patients in Florida and elsewhere. He hopes Gov. DeSantis will do more with PBM reform if he is reelected.

"There is a danger of people feeling like our work in Florida is done on the PBM issue," says Mr. Cantrell.

Elizabeth "Blair" Solow, MD, assistant professor of medicine in the Division of Rheumatic Diseases at UT Southwestern Medical Center, Dallas, and chair of the ACR's Government Affairs Committee, agrees and notes the Florida executive order has limitations. For example, it covers only state agency contracts, such as Medicaid and the state employee benefit plan. This means the order impacts only a portion of Florida's population and "can easily be undone" by a new administration, she says.

"It is imperative that Florida enact legislation to codify these protections and expand them to all Floridians," Dr. Solow says.

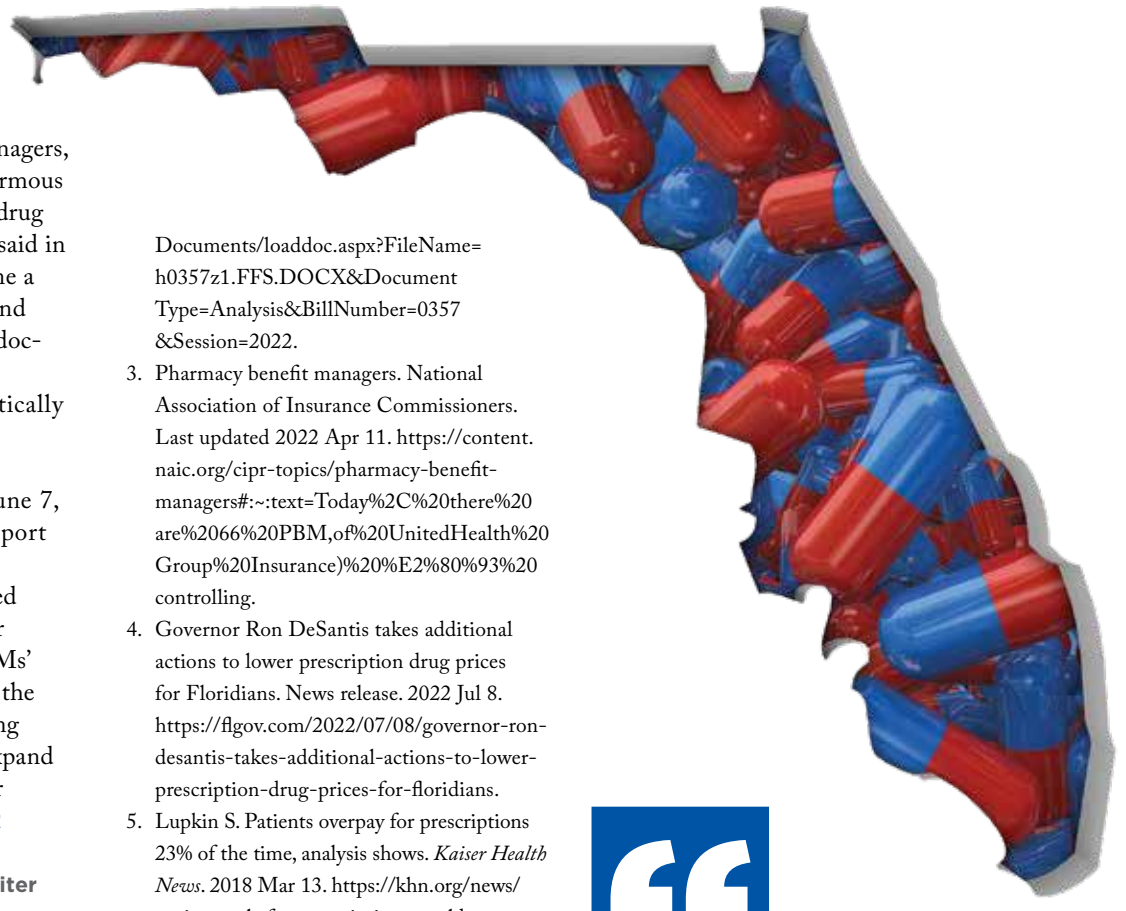
At the national level, the Federal Trade Commission (FTC) is seeking records from six of the biggest players in the industry as part of an investigation into PBM practices.

"Although many people have never heard of pharmacy benefit managers, these powerful middlemen have enormous influence over the U.S. prescription drug system," FTC Chair Lina M. Khan said in a June 7 release. "This study will shine a light on these companies' practices and their impact on pharmacies, payers, doctors and patients."[6]

The probe will examine how vertically integrated PBMs affect access and affordability of prescription drugs, according to the release. Also on June 7, the ACR issued a statement in support of the FTC action.

"The FTC investigation announced today is a critical step toward greater transparency and oversight over PBMs' opaque business practices, as well as the enactment of meaningful drug pricing reforms that will reduce costs and expand access to important therapies for our patients," states the ACR release.[7] **R**

Catherine Kolonko is a medical writer based in Oregon.



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'I don't want to undersell an improvement, but $10,000 isn't even pocket change for PBMs,' Mr. Cantrell notes.

ACR Praises House of Representatives for Passing Much-Needed Prior Authorization Reform Bill

FROM THE COLLEGE

WASHINGTON, D.C.—On Sept. 14, the ACR praised the House of Representatives for overwhelmingly passing bipartisan legislation intended to make it easier for Medicare Advantage beneficiaries to access the timely care they need.

The Improving Seniors' Timely Access to Care Act (H.R. 3173) passed the House on a voice vote. If enacted, the bill will create more transparency and accountability under Medicare Advantage and establish important guardrails around prior authorization, an insurance approval that often results in delays or denials for doctor-prescribed treatments. To help ensure patient care is not needlessly disrupted, the legislation would establish an electronic prior authorization process and require the federal government to create a process for "real-time decisions" for treatments that are routinely approved.

"We applaud the House of Representatives for passing the Improving Seniors' Timely Access to Care Act by a wide margin," said Kenneth G. Saag, MD, MSc, president of ACR. "For too long, prior authorization policies have disrupted rheumatology patients' access to the care they desperately need, prolonging their pain and leading to worse health outcomes. In order to protect patients with serious, chronic diseases, prior authorization must be reined in and safeguards established."

Since its introduction by Representatives Suzan DelBene (D-WA), Mike Kelly (R-PA), Ami Bera (D-CA) and Larry Bucshon (R-IN), the bill gained broad support from both sides of the aisle and garnered over 300 cosponsors. The bill now advances to the Senate, where Senators Roger Marshall (R-KS), Kyrsten Sinema (D-AZ), John Thune (R-SD) and Sherrod Brown (D-OH) have already introduced companion legislation (S. 3018). ACR urges the Senate to quickly pass the bill and send it to President Biden's desk for his signature.

"The delays and disruptions to treatment caused by the arbitrary application of prior authorization is frustrating for patients and burdensome for the country's thousands of rheumatologists and their staff who spend several hours each week completing unnecessary forms and fighting insurance companies for approval," said Blair Solow, MD, chair of ACR's Government Affairs Committee. "By voting to streamline the prior authorization process under Medicare Advantage, the House of Representatives has signaled its support for patients and providers across the country. We applaud the many legislative champions who have worked to advance this important, long-needed reform and urge the Senate to quickly pass it for President Biden's consideration."

The House passage of the Improving Seniors' Timely Access to Care Act coincides with Rheumatic Disease Awareness Month. As part of ACR's advocacy efforts on behalf of rheumatologists and patients with rheumatic disease, nearly 100 advocates recently met with Members of Congress to discuss why legislative reforms, including H.R. 3173, are needed to ensure that necessary care is not disrupted by insurance practices such as prior authorization.

According to a 2021 American Medical Association (AMA) survey, 93% of physicians report care delays arising for patients due to insurer's prior authorization requirements. The survey also found that over one-third of physicians (34%) say prior authorization has led to a serious adverse event for a patient in their care. **R**

A Case of Nodular Rash & Painful Joints

A rare instance of cutaneous PAN

■ BY VANIA LIN, MD, MPH, REBECCA JOHNSON, MD, & LISA SUTER, MD

DR. LIN

DR. JOHNSON

DR. SUTER

Most cases of cutaneous PAN are idiopathic, but up to 40% may be associated with infection, as well as inflammatory bowel disease & long-term exposure to minocycline.

Polyarteritis nodosa (PAN) is a necrotizing vasculitis, predominantly involving medium-sized arteries, that causes systemic disease, and, less commonly, cutaneous-limited disease. The population prevalence for PAN ranges from 2 to 33 per million.[1-3] Estimates vary due to the increased recognition and classification of other forms of vasculitides over time and variation in the regional prevalence of hepatitis B virus infection, a disease that is closely associated with PAN. Cutaneous PAN accounts for approximately 4% of all cases of PAN.[4]

Here, we present a case of cutaneous PAN with antecedent group A *Streptococcal* infection, treated with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, prednisone and antibiotics.

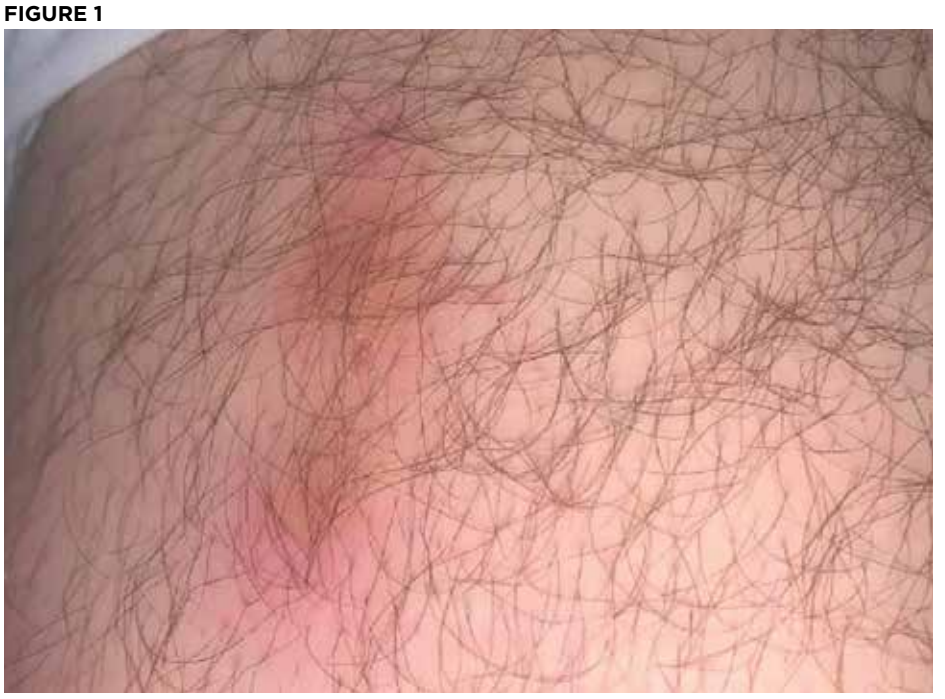
Case Description

A 22-year-old man with a past medical history of gastric sleeve surgery and active tobacco use presented with a painful rash and polyarthralgia. His rash had started four weeks before on the sole of his left foot and spread in an ascending manner, involving both lower extremities, his groin region and abdomen. He developed swelling and pain in his left knee two weeks before and pain in his bilateral elbows two days before presentation. He was febrile up to 102.8°F (39.3°C) the first night of his hospitalization, although the patient did not mention having a fever while at home.

The patient stated that a punch biopsy of his left calf rash had been performed by a community dermatologist a few days earlier. The tissue sample contained a muscular blood vessel associated with a mixed inflammatory infiltrate including neutrophils and eosinophils; fibrinoid and basophilic material within the lumen of the blood vessel and fibrosis were noted. The interpretation was of medium vessel vasculitis, suggestive of PAN, with differential diagnosis including anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and vasculitis caused by another rheumatic disease, less likely erythema induratum. The patient had been directed to come to the hospital for further evaluation.

The patient did not recall any preceding acute illnesses, vaccinations, animal or insect bites, travel or sick contacts. He denied any history of skin, joint, gastrointestinal, autoimmune or sexually transmitted diseases. He reported being predominantly indoors for work, though he occasionally did yard work at home. He had been taking NSAIDs, acetaminophen and tramadol for his symptoms with limited effect; he otherwise did not regularly take medications.

FIGURE 1



The patient presented with an erythematous, tender, nodular rash overlying both of his lower extremities and lower abdomen.

He denied any of the following symptoms: sore throat, cough, nasal congestion, hearing loss, chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea, numbness, tingling, muscle pain or weakness, genital discharge, dysuria and hematuria. The patient reported living with his wife and newborn baby. He denied any use of illicit drugs. He also denied any family history of psoriasis, inflammatory bowel disease, thyroid disease, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus and other autoimmune disease.

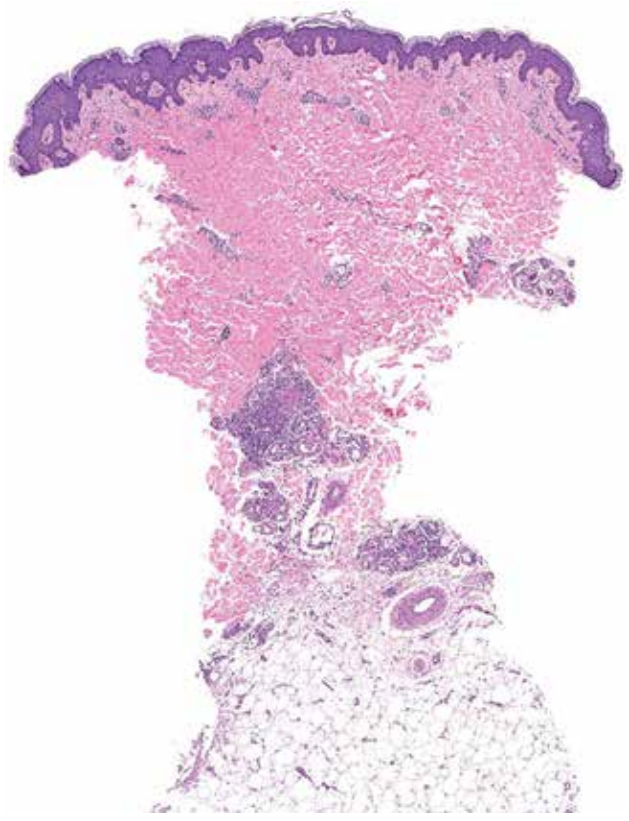
The patient's physical exam was notable for normal cardiac, pulmonary, abdominal and neurological exams; an erythematous, tender, nodular rash overlying both lower extremities, the mons pubis and lower abdomen (see Figure 1, above); tenderness without overt synovitis in both elbows; and a warm effusion of his left knee.

Extensive diagnostic testing was performed. Notable findings included normal renal function; elevated alkaline phosphatase at 125 U/L (reference range [RR]: 9–122 U/L) with normal bilirubin, AST and ALT; leukocytosis with 17.9x10^3 cells/µL white blood cells (WBC; RR: 4.0–11.0x10^3 cells/µL); and neutrophilia with absolute neutrophil count of 13.24x10^3 cells/µL (RR: 2.00–7.60x10^3 cells/µL); mild anemia with hemoglobin of 12.4 g/dL (RR: 13.2–17.1 g/dL); thrombocytosis with platelet count of 498x10^3 cells/µL (RR: 150–420x10^3 cells/µL); and elevated, high-sensitivity C-reactive protein of 234.5 mg/L; normal procalcitonin and elevated anti-streptolysin O (ASO) titer of 959 IU/mL (RR: ≤200 IU/mL).

Tests were negative for COVID-19, group A *Streptococcus*, urine chlamydia and gonorrhea, syphilis, QuantiFERON, Lyme antibody, *Rickettsia* IgG and IgM, hepatitis B surface antigen, hepatitis B total core antibody, hepatitis C antibody and human immunodeficiency virus. Parvovirus DNA was not detected by polymerase chain reaction (PCR). Blood cultures failed to identify a pathogen.

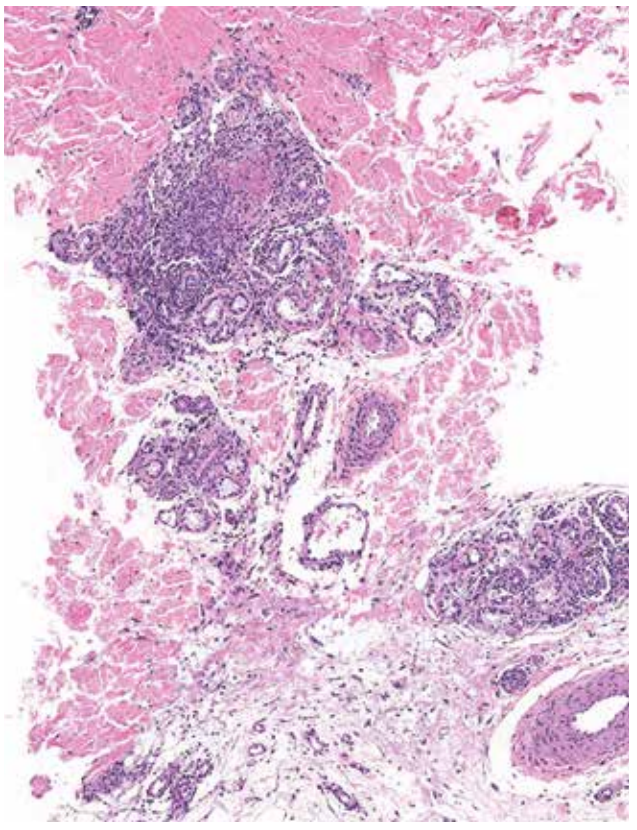
Rheumatoid factor was mildly positive at 17 IU/mL (RR: <14 IU/mL); anti-nuclear antibody (ANA) was 1:80, dense and fine speckled (RR: <1:80); angiotensin-converting enzyme (ACE) was normal. ANCA, myeloperoxidase antibodies (MPO), proteinase 3 (PR3) and cryoglobulin tests were negative. C3 and C4 were normal. Urinalysis returned 1+ protein and 1+ ketones; urine

FIGURE 2A



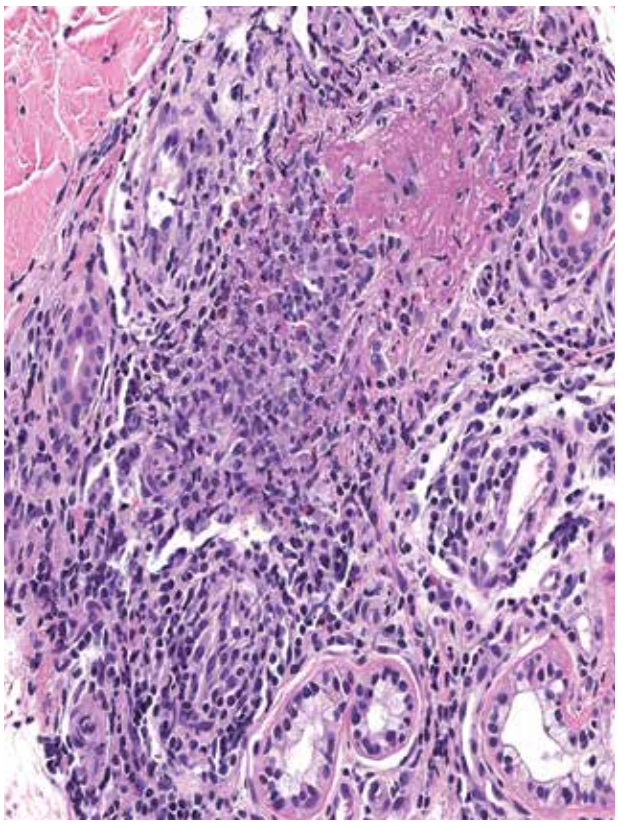
Punch biopsy demonstrates an uninvolved epidermis with focal mid to deep dermal vasculocentric inflammation (H&E stain, 2x).

FIGURE 2B



Mid to deep dermal vasculocentric mixed inflammation with relatively unaffected deep dermal vessels (H&E stain, 10x).

FIGURE 2C



Vasculocentric inflammation consisting of lymphocytes, histiocytes, neutrophils, and eosinophils with obscuration of vessel walls and fibrin deposition (H&E stain, 20x).

protein/creatinine was 0.10 mg/1.0 mg (RR: <0.10 mg/1.0 mg). Serum protein electrophoresis was normal, and serum free kappa/lambda was absent.

Chest X-ray and transthoracic echocardiogram were unrevealing.

Left knee joint aspiration yielded turbid, yellow synovial fluid, with 10,301 nucleated cells/μL (RR: ≥2,000 nucleated cells/μL is classified as inflammatory synovial fluid), less than 3,000 red blood cells and no crystals. Synovial fluid culture did not yield an organism.

The patient was evaluated by a dermatologist, who felt his cutaneous lesions were likely consistent with cutaneous PAN, which may be associated with group A *Streptococcal* infection. Differential diagnosis included panniculitis (including erythema nodosum, which may also be associated with group A *Streptococcal* infection, but would appear as septal panniculitis rather than medium vessel vasculitis; and erythema induratum, which may be associated with tuberculosis), ANCA-associated vasculitis, subcutaneous nodules of rheumatic fever and atypical infection. A repeat punch biopsy of the patient's rash was performed.

The patient was started on treatment for rheumatic fever with 10 days of cephalexin because he met the 2015 American Heart Association revised Jones major criterion of subcutaneous nodules and minor criteria of polyarthralgia, fever of ≥38.5°C and a CRP ≥3 mg/dL. He was also started on ibuprofen and colchicine for suspected cutaneous PAN. (*Note*: Penicillin was avoided due to the patient's drug allergy.)

The skin biopsy performed during the patient's hospitalization showed vasculocentric inflammation of the medium-sized vessels and relative sparing of the small vessels in the mid and deep dermis, with an inflammatory infiltration composed of lymphocytes, histiocytes, neutrophils and eosinophils in the vessel walls and fibrin obscuration of vessel lumina (see Figures 2A–C, above). These results were consistent with medium vessel vasculitis, with ANCA-associated vasculitis in the differential diagnosis.

The skin tissue culture grew 1+ coagulase-negative *Staphylococcus*, which was thought to be a contaminant. Because the patient developed new skin lesions despite the aforementioned therapy, the dermatologist recommended adding prednisone at a dose of 0.5 mg/kg daily, with planned taper over 28 days. The patient was discharged following clinical improvement on steroids, with outpatient rheumatology and dermatology follow-up.

Discussion

PAN is a rare, necrotizing, predominantly medium-vessel vasculitis first described in 1852, with its cutaneous-limited form described in 1931. Characteristic histopathology of cutaneous PAN is leukocytoclastic vasculitis in small- to medium-sized arterioles of deep dermis or hypodermis, with or without fibrinoid necrosis. Most cases of cutaneous PAN are idiopathic, but up to 40% may be associated with infection (group A *Streptococcus*, hepatitis B, hepatitis C, recurrent urinary tract infections, parvovirus B19 and *Mycobacterium tuberculosis*), as well as inflammatory bowel disease and long-term exposure to minocycline.[5,6]

Given the rarity of cutaneous PAN and its predominant distribution among individuals in their 40s or 50s, we considered a wide differential diagnosis for this patient when carrying out our evaluation, including infectious (e.g., disseminated gonococcal infection, syphilis, parvovirus B19 infection, Lyme disease, Rocky Mountain spotted fever, infective endocarditis, septic arthritis, tuberculosis), post-infectious (e.g., reactive arthritis, acute rheumatic fever) and rheumatological (e.g., ANCA-associated vasculitis, cryoglobulinemia, polyarteritis nodosa, sarcoidosis, rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, crystalline arthritis) etiologies.[5]

He was ultimately diagnosed with cutaneous PAN via skin biopsy, with high-titer ASO suggestive of antecedent group A *Streptococcal* infection and possible subsequent rheumatic fever, and his treatment was tailored to this diagnosis. He had no apparent deep organ involvement to suggest a systemic vasculitis. Continued monitoring and heightened awareness are important moving forward, given the often chronic and relapsing course of cutaneous PAN and possible progression to systemic PAN. R

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Disclosures

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SONOGRAPHIC DIAGNOSIS OF KNUCKLE PADS

Differentiating from other conditions

■ BY PANKAJ BANSAL, MD, RHMSUS, EUGENE KISSIN, MD, RHMSUS, & FAWAD ASLAM, MBBS, RHMSUS, RMSK

Musculoskeletal ultrasound can be a useful tool in diagnosing knuckle pads & ruling out other etiologies.

In Brief

Musculoskeletal ultrasound can play a role in differentiating knuckle pads—benign, subcutaneous, soft-tissue nodules—from more serious conditions.

The Case

A 56-year-old white woman was evaluated for a one-year history of painless bumps on the dorsal aspect of the proximal interphalangeal (PIP) joints of both hands and suspected flexor tenosynovitis in her palms. On examination, small cystic nodules without erythema or tenderness were present on the dorsal aspect of several PIP joints (see Figure 1, below). The PIP joints had normal range of motion and no swelling or tenderness. She had induration along the course of the third flexor tendon without frank triggering or contractures. Hand radiographs were normal.

A musculoskeletal ultrasound examination was performed to assess for synovitis and tenosynovitis and to evaluate the nodules on the PIP joints and the palms. The ultrasound demonstrated the underlying third PIP joint and extensor tendon were normal, but it revealed a cystic, semilobulated lesion with hypoechoic and isoechoic features, which was partially compressible (see Figures 2 and 3, opposite) and exhibited a mild (grade 1) Doppler signal.

FIGURE 1

Knuckle pads over the proximal interphalangeal joints.

ZAYACSK / SHUTTERSTOCK.COM

An evaluation of the palmar aspect of the right hand revealed an ill-defined hypoechoic lesion superficial to the flexor tendon proximal to the third metacarpophalangeal (MCP) joint (see Figures 4 and 5, opposite). It did not move with the underlying tendon, and the lesion had no Doppler signal. The underlying flexor tendon, the MCP joint and the A-1 pulley were normal. Diagnosis of PIP joint knuckle pads, in association with Dupuytren's contracture, was made. No further intervention was recommended.

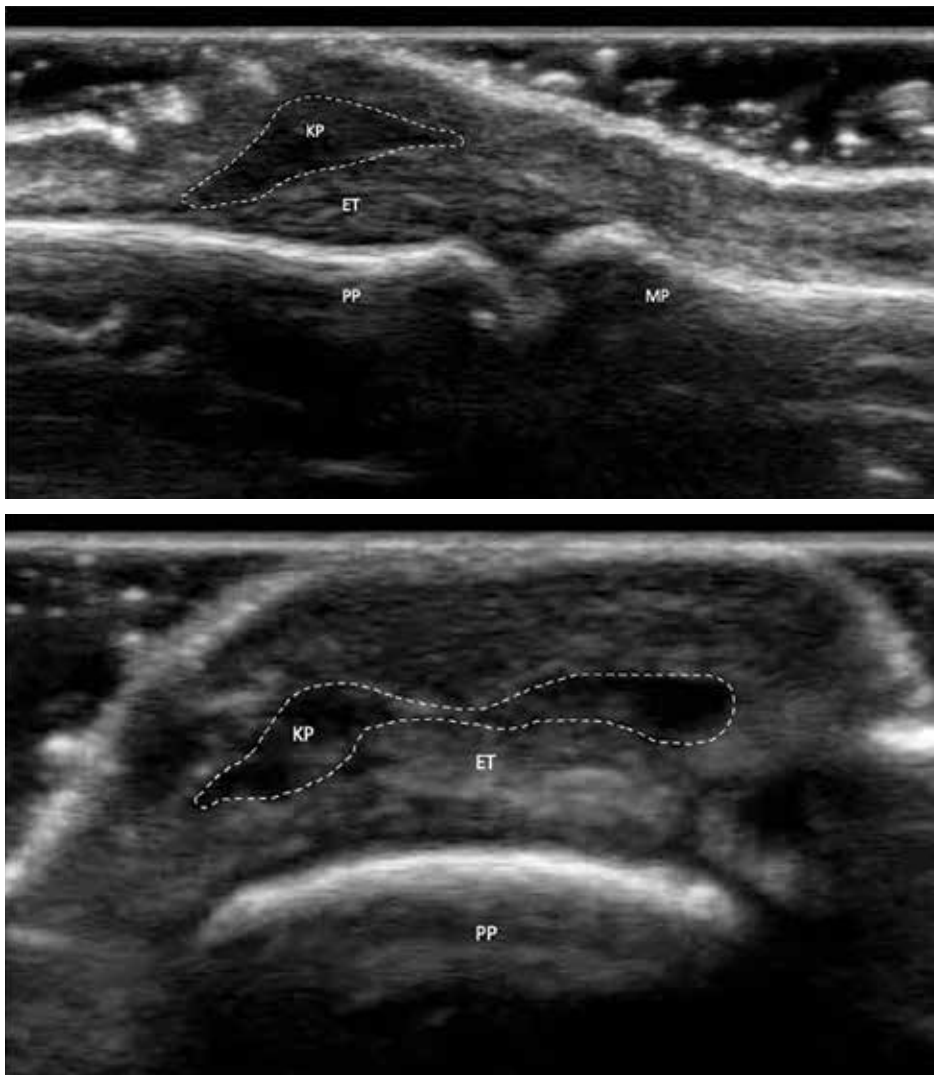
Discussion

Knuckle pads are benign subcutaneous nodules on the dorsal aspect of the PIP joints. Rarely, they are seen on the dorsal aspect of the MCP joints.[1] These fibrofatty nodules can be bilateral and are painless. Knuckle pads are usually idiopathic, although rare associations have been reported with repeated trauma and Dupuytren's contractures.[2-4] They are not associated with underlying joint or tendon abnormalities.

No intervention is needed for these benign nodules. They usually come to the physician's attention for cosmetic reasons or due to concerns of arthritis. An accurate diagnosis should be made after excluding other causes, such as gouty tophi, rheumatoid nodules, ganglion cysts, Bouchard nodes, synovitis and other rarer causes of nodules, such as multicentric reticulohistiocytosis.

Musculoskeletal ultrasound can be an important tool in confirming the diagnosis of knuckle pads. On gray-mode sonography, knuckle pads are hypoechoic, subcutaneous masses with ill-defined margins that are usually non-compressible.[5] Doppler usually does not show any hypervascularity in the nodule, although peripheral hypervascularity has been rarely reported.[6] The underlying joint and tendon are usually normal. Histopathology of knuckle pads reveals myofibroblast

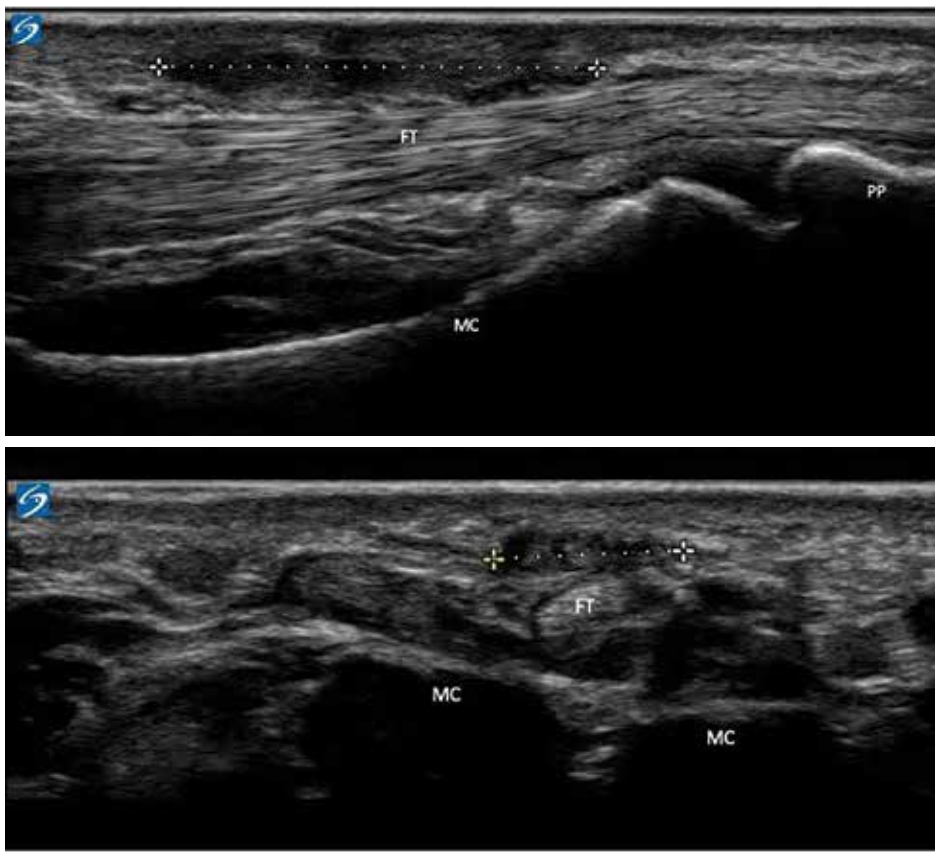
FIGURES 2 & 3



Dorsal longitudinal and transverse B-mode ultrasound views of the knuckle pads. Subcutaneous hypoechoic mass can be seen (enclosed in dotted lines).

***Key:* MC: metacarpal; PP: proximal phalanx; ET: extensor tendon; KP: knuckle pad.**

FIGURES 4 & 5



Palmar longitudinal and transverse B-mode ultrasound views of the Dupuytren's contracture. An ill-defined hypoechoic lesion superficial to the flexor tendon proximal to the metacarpophalangeal joint can be seen (dotted line).

Key: MC: metacarpal; PP: proximal phalanx; MP: Middle phalanx; FT: flexor tendon.

proliferation and decreased elastic filaments in the dermis. The epidermis and corneum are normal.[5]

Similar to our case, knuckle pads in association with Dupuytren's contractures have been reported.[2] Dupuytren's contractures are secondary to fibrous thickening of the palmar fascia, leading to firm palmar nodules and cords. On musculoskeletal ultrasound, these subcutaneous nodules in the palmar fascia are directly superficial to the flexor tendons and appear hypoechoic. Hypervascularity on color Doppler is usually absent and the lesions are non-compressible. Typically, the length of these lesions is greater than the width.[7]

In contrast, flexor tenosynovitis of the flexor tendons of the hands appears as a hypoechoic or anechoic compressible swelling around the tendon (i.e., visible both above and beyond the tendon) with increased color Doppler signal and is accompanied by thickening and loss of the normal fibrillar pattern of the tendon.[8]

Gouty tophi can also appear on the dorsal, as well as the volar, aspect of the PIP joints. They are usually soft to firm and non-tender. Sonographically, they are heterogeneous and can be multilobulated.[9] They can contain hyperechoic calcifications with acoustic shadowing.[10] The underlying joint may reveal a double contour sign secondary to crystalline deposition on the cartilage surface.[11] Juxta-articular erosions may also be seen underneath the tophaceous deposits.[9,12] Hypervascularity can be seen around the periphery of the tophus.

Rheumatoid nodules are also painless, soft to firm, non-tender nodules and can appear on the dorsal or volar aspect of the PIP joints. Sonographically, they are homogenous hypoechoic nodules with hyperechoic rims and may have anechoic centers.[10] Features of synovitis, such as synovial hypertrophy, effusion and hypervascularity with increased color Doppler uptake, may be present. In addition, periarticular erosions can also be seen, although the nodules themselves are less erosive to the bone, and cortical bone is easily seen underneath the nodule.[10]

Synovitis of the PIP joints can also mimic knuckle pads. In contrast to knuckle pads, synovitis is associated with pain, tenderness and limited mobility of the PIP joint. Ultrasound reveals effusion, synovial hypertrophy and increased color Doppler signal in the PIP joint.

Ganglion cysts are usually soft, non-tender cystic to firm swellings and can be present, rarely, on the dorsal aspect of the PIP joints. On musculoskeletal ultrasound, they are anechoic to hypoechoic with increased posterior acoustic enhancement.[13] Ganglion cysts are usually seen in proximity to underlying tendons and can originate from the tenosynovium of the tendon. Power Doppler does not usually reveal hypervascularity, and the joint underneath is normal.[10]

Bouchard nodes are firm to hard, non-tender nodules seen on the dorsal aspect of the PIP joints in osteoarthritis. Ultrasound usually reveals underlying osteophytes and can reveal joint effusion. Erosions can be detected by musculoskeletal ultrasound in erosive osteoarthritis.[14]

In Sum

Knuckle pads are benign, subcutaneous, soft-tissue nodules. Musculoskeletal ultrasound can be a useful tool in diagnosing knuckle pads and ruling out other etiologies. **R**

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An Interview with Dr. Gary Hoffman

Committed to lifelong learning, curiosity, humility & a willingness to lose sleep

BY JASON LIEBOWITZ, MD

DR. HOFFMAN

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.

Gary Hoffman, MD, MS, MACR, is a professor of medicine at the Cleveland Clinic. After beginning his career at Dartmouth-Hitchcock Medical Center, Lebanon, N.H., in the U.S. Army and at the Mary Imogene Bassett Hospital, Cooperstown, N.Y., he joined Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), at the National Institutes of Health (NIH) as the head of the Vasculitis and Related Diseases Section from 1986–92.

In 1992, Dr. Hoffman became chair of the Department of Rheumatic and Immunologic Diseases (1992–2008) at the Cleveland Clinic, where he held the Harold C. Schott Endowed Chair. He is the founder of the Cleveland Clinic Center for Vasculitis Care and Research, founder and past chair of the International Network for the Study of the Systemic Vasculitides (INSSYS) and professor emeritus of medicine at the Cleveland Clinic Lerner College of Medicine.

He has led investigations of new therapies for vasculitis and coordinated INSSYS-based multi-center studies of diagnostic laboratory and imaging tools to assess vasculitis disease activity.

He has received the NIH Director's Award, the NIAID Director's Award, Wegener's Foundation Award, the William Ischmael Award, the Pemberton Award, the Ira Goldstein Memorial Lecture Award (NYU), the Sam and Maria Miller Award for excellence in clinical research and others.

Dr. Hoffman is a former ACR Board member, was the 2010 ACR Distinguished Clinical Investigator and is a Master of the ACR.

***The Rheumatologist (TR):* In your opinion, what makes for a master clinician?**

GH: I don't know about *master*, but anyone entrusted with another's healthcare has responsibilities I hope we all embrace: lifelong learning, curiosity, humility and a willingness to lose sleep over difficult, unsolved problems. I remember a mentor telling me, when I was a medical student: 'It is important to not get too close to patients.' That was terrible advice. As a patient, I want to feel close to my doctor and to know that, if my problems are unresolved, they care and will be losing sleep over me.

When I was in my residency and fellowship at Dartmouth, we had little to offer some patients with autoimmune diseases, such as progressive systemic sclerosis and even rheumatoid arthritis. Those were the days of gold injections and penicillamine, drugs that caused much toxicity and had modest, if any, benefit. Many patients in our waiting rooms had wheelchairs or other assistive devices, had scars over joints that were the objects of failed surgeries and had reason to lose hope. It was also the early days of joint replacement.

Josh Burnett, MD, was my senior clinical mentor. He was the first rheumatologist in New Hampshire and among the first formally trained rheumatologists in the U.S., having spent six months at Massachusetts General Hospital. I can remember more than a few patients telling him something to the effect of, 'Dr. Burnett, I am so sorry you have to deal with all my problems and have such poor treatment options.' Josh was a towering, sweet man. He would hold patients' hands, which always looked so small in his, and tell them he was there for them and would help however he could, especially for those ailments/comorbidities that could be treated more effectively. He was my hero. He was beloved and taught me more than I can express about the humanity of being a doctor.

Josh also taught me about mentoring beyond medicine. He frequently had us over for dinner and made sure to learn about the fellows with respect to our spouses, significant others, passions, problems and goals. We also learned about him and his family. These were special times that enhanced our investment in each other and I think made us a happier and more effective rheumatology division.

Josh and Edward (Ted) Harris, MD, encouraged me to spend time with surgical and rehabilitation consultants. I went to operating rooms, watched surgeries and became involved with rehabilitation, later even becoming director of a rehabilitation/physical therapy unit. These colleagues were wonderful teachers who taught me how they were helping my patients, and they also showed the limitations of their practices.

I continued that approach with surgeons for my vasculitis patients who were undergoing vascular bypass, subglottic, tubular airway and sinus surgeries. Not only did I learn, but almost without exception, whenever I called them with urgent problems, my patient and I were rewarded with prompt and friendly responses. It was so much fun! It is sad to see how little time is allowed for this kind of team relationship building in today's ultra-busy practices.

During these years my research was all over the map, driven by patient problems that were confusing, and led to literature reviews and new questions about lupus and pregnancy, antiphospholipid antibodies, myositis, calcium oxalate arthropathy in renal failure, pelvic/musculoskeletal tumors masquerading as hip pain and septic bursitis. Not focusing on a single subject will not create a foundation for an academic career, but it made me feel like a more effective doctor, and I thoroughly enjoyed it.

Tony Fauci recruited me to join the vasculitis program at the NIH in 1986. As a clinician-investigator, now with unprecedented opportunities to collaborate with like-minded people in other specialties and basic scientists and epidemiologists, I was ecstatic. I made many friends with lab-based colleagues interested in anti-neutrophil cytoplasmic antibodies and mechanisms of vascular and pulmonary injury, vessel growth and differentiation, and clusters of patients with granulomatosis with polyangiitis that raised questions about environmental triggers. It was like being a kid in a candy store. I will always be grateful to Tony for hiring me and being a friend and mentor.

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TR: **What lessons have you learned from patients that have contributed to your own growth as a clinician?**

GH: Someday, unfortunately, we will all be patients. Some of us will become victims of life-threatening diseases. When I think about patients with crippling musculoskeletal and autoimmune diseases or those with large or small vessel vasculitis, what stands out most is their resilience and courage. Most people find the will to fight, to survive and restore their lives as active students, spouses, friends and workers. I have witnessed this so many times, from children to the very elderly. It is inspiring and deserving of our respect and admiration.

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?**

GH: One has to accept that, even if we are thought to be experts by our peers, our fund of knowledge is profoundly limited. Medical mysteries are not rare, whether they be a new variation on a familiar theme or, less often, an unrecognized, new disease. Fortunately, literature searches are far easier today than going to *Index Medicus* (some old-timers may remember that). Depending on the pace of disease progression and severity of illness, one may or may not have time to review the literature.

Depending on consultations should not be considered a sign of weakness. Under the best of circumstances, you may even want to set up a brainstorming session with colleagues. I am not hesitant to do this with colleagues at my institution or in other institutions and am always flattered when someone calls me for advice.

I recommend you pick up the phone or have a problem-solving meal with colleagues. Do not underestimate how sharing a meal, especially in your own home, can promote bonding and may solve medical mysteries.

TR: **How do you approach the concept of uncertainty when entertaining a diagnosis for a patient?**

GH: In medicine in general, and especially in rheumatology, uncertainty is a familiar companion. One example of uncertainty is a patient with an 'undifferentiated' disease phenotype. Those are interesting situations. If the duration of illness is brief and there has been no recognized pattern of end-organ damage, patients should know that diseases often evolve and may not present as a fully developed picture. An illness may become more obvious and dictate a specific therapy or may even regress and resolve and be self-limiting. Patients need to know this and be reassured that you (and consultants, if necessary) will be available to follow this process and change course as needed. In the meanwhile, you will be offering symptomatic therapy and monitoring them for any new subtle, as well as serious, developments.

Patients often have more pressing questions: *How did I get this? Will it go away? When can I return to work? How likely is it for my children to have this? Will these meds provide remission? Can it be fatal?* I think we have to be transparent with our patients when the answers are not certain. They deserve nothing less. **R**

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.

I think we have to be transparent with our patients when the answers are not certain.

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An Update from the RheumPAC Chair on the 117th Congress

BY HOWARD BLUMSTEIN, MD

With the August recess over and only a couple months left in the legislative calendar for the 117th Congress, ACR staff and the Government Affairs Committee have continued to advocate and engage with members of Congress, while RheumPAC has been working to ensure that individual legislators understand what you, your practice, your patients and others in the rheumatology community face when it comes to delivering high-quality care to those with rheumatic diseases.

As the only federal political action committee (PAC) dedicated solely to the interests of rheumatology, RheumPAC continues to educate members of Congress and is always in need of additional resources to compete with those who have conflicting interests. Read on to learn about all the important work that has been done, and consider donating at **www.rheumpac.org** to help ACR advocacy efforts.

Congress has recently pivoted to considering a series of large packages consisting of multiple policies rather than its traditional bill-by-bill legislative process. The ACR and RheumPAC have taken part in those discussions to push for policy beneficial to rheumatology while pushing back on proposals that would hinder our ability to deliver care. Key provisions in some of the big bills you may have heard about in the news have:

- Placed a cap on patient Medicare Part D out-of-pocket costs at $2,000 annually;
- Expanded eligibility for low-income Medicare Part D subsidies;
- Provided no-cost vaccines under Medicare Part D;
- Limited Medicare Part D premium growth to <6%;
- Allowed Medicare to have the ability to negotiate prices with pharmaceutical companies,** and
- Put a cap on cost-sharing for qualified users of the Affordable Care Act.

In addition to those larger packages, we have been working fervently behind the scenes on other key provisions of the ACR's policy priorities. These efforts have:

- Resulted in funding for the Pediatric Subspecialty Loan Repayment Program for the first time. Money has been appropriated to get this program launched, and the ACR continues to push for additional resources to help grow the pediatric workforce through loan forgiveness;
- Averted 10% cuts to Medicare reimbursement at the end of 2021. Although certain aspects of those cuts have been phased back in, the ACR has actively advocated against them and expects they will be addressed before the end of 2022; and
- Garnered nearly 400 Congressional co-sponsors on federal legislation to reform prior authorization; the bill was passed by the House via voice vote and is now before the Senate, where the ACR is pushing for its passage.

The ACR and RheumPAC have also been educating members of Congress and building bipartisan support for several other proposals, including:

- Growing the medical workforce by:
  - Repealing the cap on Medicare-funded residency slots;
  - Transferring more than 30,000 Congressionally approved J1 visas to medical professionals; and
  - Deferring interest on medical student loans while in residency;
- Mitigating step therapy protocols;
- Banning copay accumulator policies;
- Expanding the use of telehealth by making many of the rules instituted during the pandemic permanent;
- Investigating pharmacy benefit manager practices to address their role in the rising cost of drugs; and
- Increasing NIH, NIAMS and CDC research funding for rheumatic diseases, as well as securing dedicated funding for arthritis through the U.S. Department of Defense.

As you can see, it has been a busy year in Congress and of advocating for policies that can positively address the issues that impact rheumatology care providers and their patients.

Let us work on your behalf, and give us the resources to increase the ACR's impact on decisions in D.C. Make your investment today: **www.rheumpac.org**. **R**

Howard Blumstein, MD, is a rheumatologist at Rheumatology Associates of Long Island and chair of RheumPAC.

**The ACR continues to work with Congress and will work with regulatory agencies to ensure physicians, practices and patients are not in the middle of negotiations between the government and drug manufacturers that will hurt access to Part B medications. The ACR is also proposing exempting Part B reimbursements from sequestration reductions.

After an inadequate response or intolerance to TNF blockers in adults with moderate to severe RA[1]

Not an actual patient.

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.

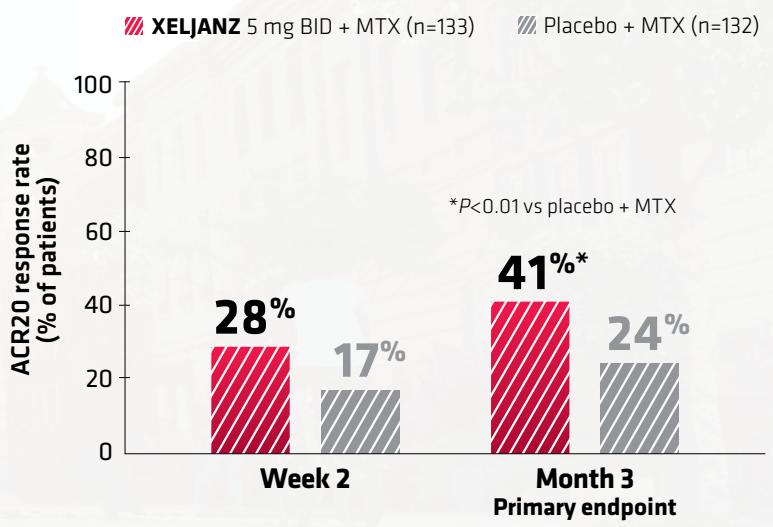
†UC=ulcerative colitis. XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active UC, who have had an inadequate response or intolerance to one or more TNF blockers. Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biological therapies for 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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XELJANZ® (tofacitinib)/XELJANZ XR/XELJANZ Oral Solution

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

Let's Stay Humble, Folks

Milk of urate bulla

BY SAMANTHA C. SHAPIRO, MD

A 60-year-old Black woman with a history of stage 3 chronic kidney disease, type 2 diabetes and hypertension presented with a 12-month history of asymmetric polyarthritis of the wrists, metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP) and knee joints.

The review of systems was unremarkable. She denied oral ulcers, rashes, alopecia, or a history of pleural or pericardial effusions. She denied a history of psoriasis, dactylitis, inflammatory back pain, uveitis, abdominal pain, melena or hematochezia. There was no history of podagra, tophi or acute monoarthritis.

Laboratory studies were notable only for a positive anti-nuclear antibody at a titer of 1:80 with a homogenous pattern, and an elevated serum urate level of 9.5 mg/dL. She had chronic creatinine elevation, normocytic anemia and proteinuria attributed to diabetic nephropathy. Extractable nuclear antigens, complement levels, rheumatoid factor and anti-cyclic citrullinated peptide were negative.

In October 2018, treatment with adalimumab and prednisone was initiated with improvement of synovitis, but the patient's disease flared upon tapering of the glucocorticoids. In July 2019, she presented to the clinic in tears, with acute monoarthritis of the right knee. She was unable to bear weight.

Arthrocentesis revealed inflammatory synovial fluid with 40,000 white blood cells/μL (neutrophil predominant). Gram stain, bacterial cultures and crystals were negative. She responded positively to glucocorticoids. Over the next year, her disease remained active in the hands, feet and knees, with minimal response to etanercept, tofacitinib or tocilizumab.

In October 2020, the patient returned to the clinic with hard, sub-centimeter, white lesions on her finger pads. A warm effusion of her left first MTP joint and a white blister on her left second toe were also noted on examination (see Figure 1, right). There was no sclerodactyly, Raynaud's phenomenon or muscle weakness. Nailfold capillaries, muscle strength and creatinine kinase levels were normal.

Aspiration of the first MTP joint and blister yielded 5 cc of chalky white fluid (see Figure 2, right). Polarized light microscopy revealed negatively birefringent crystals consistent with monosodium urate. Her serum urate level was 9.7 mg/dL. Repeat radiographs of both hands and feet showed interval erosive changes in both midfeet, consistent with gouty arthropathy.

Allopurinol was initiated and titrated to a goal serum urate of less than 6.0 mg/dL, per the 2020 ACR Guideline for the Management of Gout.[1] Five milligrams of prednisone by mouth daily was continued as flare prophylaxis.

Over the next several months, inflammatory arthritis and subcutaneous lesions resolved. Biologic therapy was stopped without recurrent disease flare.

Discussion

The differential diagnosis of seronegative inflammatory arthritis is broad, and this patient challenged us to review it at every visit. On presentation, seronegative rheumatoid arthritis or peripheral seronegative spondyloarthropathy was believed to be the most likely given her chronic, subacute, asymmetric polyarthritis with predominant hand involvement. When the patient developed acute monoarthritis of the right knee, septic and crystalline arthritis were considered. However, synovial fluid studies argued against both, especially given the absence of crystals. Over the course of the next year, polyarthritis failed to respond to three different classes of biologic medications. Glucocorticoids were mildly helpful.

About three years after symptom onset, hard white lesions at the fingertips raised concern for calcinosis cutis vs. tophi. Repeat history, physical exam and laboratory studies did not support a diagnosis of systemic sclerosis or myositis. Ultimately, the white blister on the toe—a finding consistent with milk of urate bulla—confirmed her true diagnosis: chronic tophaceous gout.

Gout classically presents with episodic flares of monoarthritis. Rarely, tophi may develop in the absence of typical gout flares, mimicking other inflammatory arthritides like rheumatoid arthritis. Patients in whom this occurs tend to be older women with predominant hand involvement and chronic kidney disease, as seen in our case.[2] More rarely, milk of urate bullae may form at sites of mild trauma.[3]

As this case illustrates, there is no place for hubris in rheumatology. When patients aren't responding to standard therapies, it's our duty as rheumatology providers to reevaluate and reassess. Stay humble. The answer might be as simple as … gout. R

FIGURE 1

Milk of urate bulla

FIGURE 2

Milk of urate aspirated from the first MTP joint and milk of urate bulla

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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VASCULITIS GUIDELINES IN FOCUS

Part 6: Giant cell arteritis

■ BY MICHAEL PUTMAN, MD

This recommendation is not intended to discourage the use of ultrasound in the evaluation of patients with suspected GCA. … The guideline is intended for what's practical & accessible at the present time in the U.S.

*In 2021, the ACR—in concert with the Vasculitis Foundation (VF)—released four new vasculitis guidelines, one each on: 1) anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, 2) giant cell arteritis (GCA) and Takayasu arteritis, 3) polyarteritis nodosa and 4) Kawasaki disease (**https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis**). The guideline development process is complex. For the vasculitis guidelines, this process kicked off in June 2017, when the core leadership team formed by the ACR first met in person. The ACR also convened expert and voting panels. Together, the core team and the two panels determined the project's scope. Members of the literature review team assembled evidence using the most recent nomenclature system for vasculitis, the 2012 Chapel Hill Consensus Conference nomenclature.[1] A panel of patients contributed as well. In this series, we discuss the updated recommendations with authors who contributed to each guideline. Read previous installments in this series: **https://www.the-rheumatologist.org/?s=%22Vasculitis+Guidelines+in+Focus%22**.*

We continue our series with Mehrdad Maz, MD, an author of the ACR/VF guideline for GCA.[2] Dr. Maz is a professor of medicine, director of the rheumatology fellowship training program, and chief of the Division of Allergy, Clinical Immunology, and Rheumatology at the University of Kansas Medical Center, Kansas City, Kans.

From the guideline—*Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over temporal artery ultrasound for establishing a diagnosis of GCA.*

Q: I believe some practical considerations led to a conditional recommendation for temporal biopsy over ultrasound. Why did the panel end up on that side of the debate?

Dr. Maz: The short answer is that this recommendation is not intended to discourage the use of ultrasound in the evaluation of patients with suspected GCA. Also, the objective of this guideline was to provide evidence-based recommendations and expert guidance in the U.S. Out of 22 recommendations for GCA, only one was a strong recommendation. The remainder were conditional, including the one to consider temporal artery biopsy over the use of ultrasound of the temporal artery for diagnosis of GCA.

It's important to explain what we mean by a conditional vs. strong recommendation because it pertains to your question.

Strong recommendations are typically supported by moderate- or high-quality evidence, such as what you see in randomized controlled trials. A strong recommendation is one that would apply to all, or almost all, patients, and so only a small proportion of clinicians and patients would not want to follow the recommendation.

A conditional recommendation is supported by lower quality evidence. A conditional recommendation would apply to most patients, but the alternative is a reasonable consideration. As we go through these discussions, let's keep these definitions in mind.

The guideline is intended for what's practical and accessible at the present time in the U.S. As you know, the use of ultrasound for this purpose requires some skills, expertise and familiarity with this technique, which is currently not as widespread in the U.S. as in European countries. For this reason, we mention in the guideline that in centers where appropriate training and expertise exist, temporal artery ultrasound may be a useful and complementary tool for diagnosing GCA. We hope that as this diagnostic modality is used more often, radiologists and rheumatologists alike, in more centers develop the skills and expertise in using and interpreting ultrasound. The recommendations don't preclude the use of ultrasound; we hope to start using it eventually.

From the guideline—*Recommendation: For patients with newly diagnosed GCA, we conditionally recommend obtaining noninvasive vascular imaging to evaluate large vessel involvement.*

Q: There is a conditional recommendation for obtaining noninvasive imaging for large vessel involvement, which I don't think people are doing routinely. Is this a recommendation for universal screening, and by what modality would you recommend it?

Dr. Maz: I think you're right about the current prevalent practice. Outside of large academic centers, imaging of large vessels is not routinely considered. This is also a conditional recommendation. This idea is based on knowledge that large vessel involvement can be present with or without overt clinical manifestations. The implications of this are significant, especially for chronic management and monitoring of disease and its large vessel complications.

On the other hand, the guideline also states that in patients without large vessel involvement on initial screenings, it may or may not be necessary to perform routine or repeated monitoring with vascular imaging. Of course, it depends on clinical manifestations and symptoms while patients are followed longitudinally.

Large vessel imaging can also help with the diagnosis of GCA in the absence of cranial manifestations or in lieu of biopsy or when we are faced with a negative biopsy, but we are still concerned that patients have signs and symptoms of large vessel disease that require further evaluation, diagnosis and management.

As to what kind of modality to use, both magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are readily available and can be used for this purpose. We're not recommending conventional catheter-based angiogram for routine

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screening because it is more invasive, and MRA or CTA may provide the needed information.

From the guideline—*Recommendation: For patients with newly diagnosed GCA, we conditionally recommend the use of oral glucocorticoids with tocilizumab over oral glucocorticoids alone.*

Q: The guideline recommends tocilizumab up front. That reflects my practice and many others. Yet it differs from what EULAR recommends, which is to use only tocilizumab in high-risk situations.[3] What do you think led to the difference?

Dr. Maz: Just a reminder that this is also a conditional recommendation, and alternative approaches are still acceptable. Tocilizumab is the only FDA [U.S. Food & Drug Administration] approved therapy for GCA. Interestingly, even glucocorticoids, including prednisone, are not approved for GCA, but we're quite aware of their efficacy for GCA.

The use of tocilizumab early on is based on data from GiACTA, which showed that tocilizumab has a significant steroid-sparing effect in GCA.[4] It's conditionally recommended for initial treatment to potentially reduce side effects of chronic glucocorticoid therapy. However, methotrexate with prednisone or prednisone alone can be used for newly diagnosed patients. The decision to treat with tocilizumab and glucocorticoids, methotrexate and glucocorticoids, or glucocorticoids alone as the initial therapy should be based on the physician's experience, and the patient's clinical condition, values, and preferences.

Also, cost may be a factor with tocilizumab. Its use is affected by other factors. For instance, patients with recurrent infections or diverticulitis may not be able to use this. So other options are valid and can be used.

From the guideline—*Recommendation: For patients with GCA who have critical or flow-limiting involvement of the vertebral or carotid arteries, we conditionally recommend adding aspirin.*

From the guideline—*Recommendation: In patients with newly diagnosed GCA, we conditionally recommend against the use of a hydroxymethylglutaryl-coenzyme A reductase inhibitor (i.e., statin) specifically for the treatment of GCA.*

Q: The guidelines gave a conditional recommendation against statins and in favor of aspirin for flow-limiting involvement. Why?

Dr. Maz: This recommendation was about whether statins could be used for the treatment of GCA. The guideline's recommendations address whether they provide a significant therapeutic effect for GCA. The recommendation wasn't to address if statins are useful for patients with risks for cardiovascular events, which is a different clinical question. We know aspirin may be beneficial in preventing ischemic events, but the efficacy of aspirin in preventing ischemic events without flow-limiting stenosis of the vertebral or carotid arteries is unclear.

Theoretically, it makes sense to reduce cardiovascular risk for the management of some patients using aspirin or statins, which is what we do for other patients with risk factors. Yet the available data didn't show particular efficacy for those with this disease. Once again, being a conditional recommendation, this does not exclude their use based on the treating physician's decision and individual patient's clinical situation and risk factors.

Q: Regarding the duration of tocilizumab and glucocorticoids, there's been a lot of interest in this with ANCA-associated vasculitis and lupus, but there's been limited data. Was there any discussion on the duration of these?

Dr. Maz: There was a lot of discussion about it, but we had to look at the data behind answering this. I'm sure some readers of the guideline will have the same question and want to know about how to manage these patients. Because of a lack of long-term evidence on how long to treat these patients, the optimal duration is not determined. We were only able to present a position statement that the optimal duration of therapy is not well established and should be guided again by patient values and preferences. This was discussed among the patient panel, which emphasized minimizing the use of glucocorticoids. They recognized that relapses occurred, and patients may need to be treated longer. The physicians had a similar thought process.

Regarding the length of therapy for tocilizumab, lack of long-term follow up for tocilizumab at the time of the literature review for this guideline development influenced the decision. The first part of the GiACTA study reported the effect of tocilizumab for 12 months, but the second part extended the data for three years, with favorable responses seen in these patients.

Although we couldn't really outline length of therapy, we did mention that in patients with GCA who are in apparent clinical remission, we strongly recommended long-term clinical monitoring over no monitoring at all, which was the only strong recommendation in this guideline given the minimal risks and potential catastrophic outcomes if patients are not monitored.

The important point to emphasize here is that the goal and the vision of the ACR for this guideline are similar to other ACR guidelines. The ACR/VF vasculitis management guideline will be updated periodically to provide a timely recommendation based on new data or new therapies as they become available. **R**

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Introduction to Mentoring

How to develop critical relationships that fuel the training & career development of exceptional clinicians & clinician-scientists

BY DANIEL K. WHITE, PT, ScD, MSc, & SUSAN BARTLETT, PhD

High-quality mentoring is perhaps the most recognized ingredient to a successful career, one that remains little understood. Here, we present a brief overview of the elements of successful mentor-mentee relationships for clinicians and scientists in rheumatology. We discuss the importance of mentorship and characteristics of good mentoring, and offer our personal reflections as both mentees and mentors.

What Exactly Is a Mentor?

Mentor does not have a standardized definition. The term comes from Greek mythology. In Homer's *Odyssey*, Mentor was a character in charge of Odysseus' son Telemachus.[1] However, Athena, Telemachus' mother, disguised herself as Mentor, encouraging Telemachus to go abroad and giving him advice on how to deal with personal dilemmas.

Over time, the word *mentor* has come to mean someone who shares knowledge and gives wisdom to someone less experienced. Today, the term *mentorship* describes a two-way relationship in which one individual invests personal knowledge, energy and time to help another grow and develop to become the best and most successful they can be.[2]

Why Is Mentoring Important?

Successful mentorship fulfills several important roles. It serves as a critical bridge between didactic classroom instruction and the mastery of skills necessary to be an effective clinician and/or productive scientist. Without mentorship, the translation of high-level skills, along with the discernment to know when to apply such skills, can be lost.

Mentoring offers an opportunity to acquire *tacit knowledge*—unwritten information conveyed through interactions with colleagues, students and patients. Tacit knowledge allows us to view tasks and activities from multiple perspectives, work adroitly within complex health systems and communicate effectively within interprofessional teams.

The personal growth and development that result from mentoring lead to increased academic productivity (e.g., papers and grants, career guidance and satisfaction) and the ability to network more effectively. Successful mentors encourage independent thinking and nurture the confidence mentees need to adopt new interests and methods that can propel them in new directions.

Opportunities

The most common model of mentorship is largely informal, in which mentees approach individuals they respect and trust to seek career guidance. Meetings may occur on an infrequent basis, and goals and outcomes of the informal mentor-mentee relationship are not formalized.

Informal mentorship is very common in medicine; for example, in 2016 only 50% of surgical departments in the U.S. reported offering formal mentorship programs.[3] In rheumatology practice and research, most mentoring still occurs on an informal basis. This type of mentorship has inherent drawbacks, and the ultimate success of such partnerships has received little evaluation.

Within the rheumatology community, we are fortunate to have structured mentoring opportunities funding from the Rheumatology Research Foundation to nurture the development of future rheumatologists and rheumatology professionals interested in clinical practice and clinical research.

For short-term mentoring, the Foundation offers four-to-eight-week awards for preceptorships for medical and graduate students interested in exploring the field of rheumatology. These awards offer an opportunity for trainees to work closely with an ACR/ARP rheumatology mentor to learn about the field.

For longer-term opportunities, the Foundation offers a two-year Future Physician Scientist Award (for MD-PhD or DO-PhD candidates) and a three-year Scientist Development Award (for rheumatologists and rheumatology professionals) to pursue innovative research ideas.

Awards created by the ARP and administered through the Foundation are the Mentored Nurse Practitioner (NP) and Physician Assistant (PA) Awards for Workforce Expansion. These awards offer one-year mentorship arrangements between NP/PAs and an ACR member rheumatologist. Since its inception in 2019, 37 awardees across the U.S. and Virgin Islands have benefited from these mentorship awards.

Other opportunities for formal mentorships are available through the National Institutes of Health (NIH) in the form of K awards (e.g., K01, K12 and K23). Within institutions, T-32 grants may be available. Three-year mentoring awards are offered by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Arthritis Foundation for early career investigators in pediatric rheumatology.

Successful Partnerships

Successful mentorship, though desirable, often proves elusive. It demands an investment of time and resources, mutual respect and clear communication from both the mentor and mentee. It is helpful when both the mentor and mentee can acknowledge and share their interests, perspectives, mutual goals and preferences as part of the evaluation of overall fit.

Mentors

Mentors need to be patient while offering guidance, coaching and feedback. They need to have an altruistic spirit and exhibit a commitment to supporting the mentee's personal and professional growth and intellectual independence. Optimal mentors are often described as generous, empathetic and selfless.[4]

Active listening is a key skill used by mentors to understand what is said, as well as left unsaid because mentees are sometimes reticent to express themselves. A good mentor is aware of the common concerns about competence and finding an appropriate work-life balance that all mentees harbor and actively creates a safe environment in which mentees feel able to take risks.

A high level of emotional intelligence is helpful for mentors to discern when to listen and when to gently ask about progress or give feedback in areas that may be challenging for the mentee. Mentors also must be able to help mentees recognize their strengths and weaknesses *without judgment*, and use this knowledge to help the mentee achieve their goals.

Although professional status is important, it is not the most important prerequisite of a mentor. Rather, many mentees chose their mentors based on mutual interests or compatibility rather than professional achievements.[5]

Mentors should be reasonably well established in their own careers to have the time and ability to help mentees develop as an emerging independent investigator or clinician in their specific field of interest.

Mentors should also be prepared to help mentees create other mentoring relationships with colleagues within and beyond their setting so mentees can gain additional expertise. The notion of a *mentoring team* is increasingly popular, with the recognition of

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the value of meaningful research that results from interprofessional collaborations.

Mentees

For mentees, a critical responsibility is to be proactive. It is the mentee's responsibility to seek out and cultivate a working relationship with a potential mentor. For young clinicians, this could mean asking about how the mentor approaches specific patient populations, therapeutic treatments or techniques. For emerging scientists, this could mean preparing research questions around a specific topic or coming to meetings with data from analyses or drafts of manuscripts or abstracts.

Mentees should listen non-defensively to feedback and feel able to respond to what they have heard, either incorporating suggestions the mentor has provided or stating why certain suggestions may not have been taken.

From a broader perspective, the mentee should reflect on whether their overall goals are understood and say something if not. The mentee should feel comfortable to state when they don't understand something or don't agree with a proposed approach.

Coming Together

The first step in building a mentoring relationship is to clarify expectations with respect to time commitment, frequency of meetings, mentee needs and ground rules, such as preferred working styles of both individuals. Mentors will need to review issues and limits related to confidentiality.

Personal Reflections

Dan's Story

My first mentee-mentor relationship was as a young physiotherapist doing clinical work. I wanted to get involved with research and learned of a senior clinician at the clinic where I was working who had an active research portfolio. I spoke with him about working on a research project. Although this was an informal mentorship, it had a major impact on my decision to become a clinician-scientist.

After publishing a paper with my mentor, I enrolled in a doctoral program to gain the skills and experience needed to become an independent investigator. As a doctoral student, I had the opportunity to receive formal mentoring from my faculty advisor. We would meet regularly to work on abstracts and papers. I would send new work in advance of the meeting, and my advisor would provide valuable feedback.

After finishing my Doctor of Science degree, I started a post-doctoral fellowship within a clinical epidemiology research unit. I was unique because most of my peers were physicians. Nevertheless, the training needs of both physicians and physical therapists aiming toward a career in clinical science were the same. I needed didactic training in epidemiology and specific mentorship in my areas of interest. For the first time, I had the opportunity to be mentored by several senior scientists, and each covered a specific area of development.

When I was at Boston University Medical Campus and Boston Medical Center, my overall career mentor, rheumatologist David Felson, MD, MPH, ensured I was moving in the right direction overall. I also had two content-specific mentors. One was rheumatologist Tuhina Neogi, MD, PhD, who provided mentorship from a clinical perspective, and the other was Yuqing Zhang, MD, a methodologist who stretched my understanding of how to apply epidemiologic methods. I was also heavily influenced by biostatistician Mike LaValley, PhD.

As my area of research became more focused, I reached out to experts within these specialized fields, which helped me gain a better understanding of scientific methods and approaches to physical activity.

After taking my first tenure-track appointment, I set up my own lab and started to mentor emerging clinician-scientists. I applied what I felt worked best as a mentee, focusing on mentee-led projects that involved papers and abstracts, and set up a recurring meeting schedule to touch base with each mentee.

What has surprised me the most is how my mentees took some of my initial areas of interest and developed them into brilliant works that I could not have thought were possible.

To this day, being a mentor continues to be a very rewarding experience.

Susan's Story

My most influential mentoring experiences in rheumatology were in my early days as an instructor of medicine at Johns Hopkins University, Baltimore. During grad school and a post-doctoral fellowship, I had implemented and evaluated the effects of weight management treatments on patient outcomes, including arthritis.

An opportunity arose to create a clinical research program with Joan Bathon, MD, in the newly formed Hopkins Arthritis Center in 1998. Although this presented incredible opportunities, I also found it somewhat daunting to be an applied psychologist and researcher within the School of Medicine at Johns Hopkins while surrounded almost exclusively by rheumatologists and basic scientists in immunology.

Dr. Bathon encouraged me to apply for a newly created NIH trainee award—the K23 Mentored Patient-Oriented Career Development Award. My project was titled The Impact of Weight Loss and Exercise on Knee Osteoarthritis, and it was one of the first K23 awards given to a non-physician. My multidisciplinary mentoring team included Dr. Bathon (rheumatology), David Levine, MD, ScD, MPH (participatory research), Scott Zeger, PhD, of the School of Public Health (biostatistics), and Cynthia Rand, PhD (psychology).

This five-year K23 award afforded me the opportunity to complete the Graduate Training Program in Clinical Investigation at the Johns Hopkins School of Public Health, and gain expertise and research experience in clinical epidemiology.

Together, the protected time, additional coursework and mentoring in rheumatology positioned me well for promotion to assistant professor at Hopkins Medicine in the Division of Rheumatology. This marked the start of a successful career as an independent researcher exploring how behavior change (weight loss, exercise, treatment adherence) and addressing mood can improve the lives of people with arthritis.

In gratitude for the mentoring I received, another mentee and I petitioned the Department of Medicine at Hopkins to create the David M. Levine Excellence in Mentoring Award to formally recognize the contributions of outstanding mentors. Created more than 20 years ago, this award rapidly became one of the most valued recognitions in the Hopkins community and beyond.

I remain passionate about, and actively involved with, creating opportunities for high-quality mentoring for trainees and early career professionals. Most recently, in spring 2022, I was a co-applicant, with ARP Immediate Past President Christine Stamatos, DNP, ANP-C, and current ARP President Barbara Slusher, MSW, PA-C, on an ACR/ARP proposal to expand and coordinate mentoring activities throughout the College. The hope is to expand access to mentorship bidirectionally for all members of the College. R

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Resource

For more about the roles and responsibilities of mentors and mentees, refer to Henry-Noel et al. in the *Journal of Cancer Education*.[6]

DR. WHITE

DR. BARTLETT

Mentoring offers an opportunity to acquire tacit knowledge—unwritten information conveyed through interactions with colleagues, students & patients.

Progress on Prior Authorization Reform & More

California Rheumatology Alliance hard at work to ensure patient access to rheumatologists & the care they need

BY LINDA CHILDERS

MS. CASTRO

DR. METYAS

DR. DORE

The CRA received positive news when the California Assembly passed AB 1880.

With more than 800 members, the California Rheumatology Alliance (CRA) is one of the largest and most active state rheumatology organizations. The CRA comprises rheumatologists and rheumatology professionals from community practices and medical centers throughout California.

"Our membership encompasses all health professionals within the field of rheumatology—physicians, nurses, nurse practitioners (NPs), physician assistants (PAs), fellows currently enrolled in a California-based rheumatology training program, office managers, researchers and medical science liaisons," says Shanna Castro, the CRA's executive director.

After a two-year hiatus, the CRA held its first in-person conference since the start of the pandemic in May in San Francisco.

"Given the situation at the time of planning, we prioritized the health and safety of our faculty, attendees and exhibit partners, reducing the number of in-person attendees by 50% to ensure participants were able to reconnect with their colleagues while learning in a safer environment," Ms. Castro says.

The CRA holds a practice manager track that runs concurrently with the annual meeting, says Ms. Castro. It provides an opportunity for practice managers, supervisors and billers to network with their peers and share ideas on how to efficiently and effectively oversee a rheumatology practice.

At this year's conference, the CRA bestowed its Lifetime Achievement Award on Michael Stevens, MD, FACR, a rheumatologist at San Mateo Rheumatology. Dr. Stevens founded the CRA in 2004 and served as president of the organization from 2004–10.

Overcoming Challenges

Like many states, California is experiencing a shortage of rheumatology professionals, says current CRA President Samy Metyas, MD, MSc, FACR, FACP, a rheumatologist at the Covina Arthritis Clinic.

"We see most physicians and rheumatology staff, including NPs, PAs and others, going to work in big healthcare organizations and hospitals that can offer more money than private practices," Dr. Metyas says. "Private rheumatology practices are shrinking because of a shortage of rheumatology fellowships and training."

These shortages have also resulted in increased waiting times for patients to see a rheumatologist, he notes. "Community rheumatologists need additional help in seeing patients and running their practices efficiently."

During the pandemic, telemedicine became a popular option among rheumatologists in California, Dr. Metyas says, but it's not a replacement for traditional office visits.

"Rheumatology is based on clinical examination," Dr. Metyas says. "While telemedicine helped us to continue seeing patients during the peak of the pandemic, these visits don't replace clinical exams. In addition, some insurers aren't reimbursing telemedicine visits at the same rate as in-person visits."

Robin Dore, MD, immediate past president of CRA and a rheumatologist in private practice in Tustin, agrees.

"For some patients who are stable, telemedicine visits are fine, but in-patient appointments are vital for rheumatoid arthritis and lupus patients to determine if they're responding to therapy," Dr. Dore says.

To help increase the number of practicing rheumatologists in the state, the CRA (along with the Coalition of State Rheumatology Organizations) has given funds to the Children's Hospital Los Angeles in support of the hospital's Pediatric Rheumatology Fellowship Program. This gift is intended to serve the needs of the hospital and provide financial support to encourage physicians to practice in the field of pediatric rheumatology.

Rheumatology, like many other specialties, has faced shortages of supplies as well as people. "We've seen a shortage of many medical supplies and medications, including steroid injections and saline which we use for infusions," Dr. Metyas says.

Continuing to Advocate for Patients

The CRA has an active advocacy committee that works to ensure patient access to rheumatology care.

"CRA received positive news when the California Assembly passed AB 1880 to ensure that an appeal of a step therapy or prior authorization request must be reviewed by a clinical peer, such as a rheumatologist reviewing for a rheumatology colleague," says Tim Madden, partner at Madden Quiñonez Advocacy, who works with the CRA. "The bill is now being reviewed by the Senate. If the bill passes the Senate, it will then go to the governor in September."

Some of the bills the CRA is actively advocating for include:

- SB 958: Medication & Patient Safety Act of 2022. The CRA supports this bill, which opposes the practice of white-bagging, or requiring physicians to acquire provider-administered drugs through specialty pharmacies designated by a payer or pharmacy benefit manager. The bill prevents health plans from refusing to cover infused or injected medications the health provider has in stock if use is provided for patient safety, integrity or timely care. *This was passed by the State Senate in May but has not yet been taken up by the Assembly.*
- SB 853: Medication Access Act. The CRA supports this bill to improve patient access to medication. The bill requires health plans to cover a patient's previously prescribed drug, dose or dosage form through the duration of an appeals process in the event their health plan denies coverage. It also strengthens California's prohibition on non-medical switching, which is when a health plan forces a patient to switch from a prescribed medication to a different one for non-medical reasons. *This was held by committee in the Assembly in August.*
- AB 2352: Prescription Drug Coverage. The CRA supports this bill, which would require health plans or insurers that provide prescription drug benefits and maintain one or more drug formularies to furnish specified information about a prescription drug upon request by an enrollee or insured, or their prescribing provider. *This was passed by the Assembly in May and the Senate in August. As we go to press, it awaits concurrence.*

For information about connecting with your state or local rheumatology society, visit **https://www.rheumatology.org/Advocacy/State-Advocacy/State-Societies**. R

Linda Childers is a health writer located in the San Francisco Bay Area.

UPDATES ON PsA

Insights into the latest psoriatic arthritis treatments & research

■ BY JASON LIEBOWITZ, MD

BALTIMORE—Psoriatic arthritis (PsA) was once dismissed by some as "rheumatoid arthritis with rash." Despite that attitude, the understanding of PsA, its diagnosis and treatment, and management of comorbidities have come a long way.

At the 18th Annual Advances in the Diagnosis and Treatment of the Rheumatic Diseases, held May 13–14 at the Johns Hopkins School of Medicine, Baltimore, Ana-Maria Orbai, MD, MHS, associate professor of medicine and director of the Psoriatic Arthritis Program at the Johns Hopkins School of Medicine, began the session by discussing the latest medications that have entered the PsA armamentarium.

Medication Overview

Risankizumab is an anti-interleukin (IL) 23 monoclonal IgG1 antibody. In January, the U.S. Food & Drug Administration (FDA) approved risankizumab to treat adults with PsA. Unlike some other medications approved to treat PsA and psoriasis, the treatment dose is the same for both conditions. In terms of safety profile, some of the main potential side effects include upper respiratory tract infections, headache, fatigue, injection-site reactions and tinea infections.

The ACR20 and ACR50 response rates to risankizumab are good for the treatment of patients naive to biologics, as well as for patients with prior biologic use, noted Dr. Orbai.

In the KEEPsAKE 1 trial, 964 patients with active PsA who were intolerant to or for whom one or more conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) proved inadequate were randomized to receive 150 mg of risankizumab or placebo at weeks 0, 4 and 16. With a primary end point of an ACR20 response at week 24, the study found a significantly greater proportion of patients receiving risankizumab achieved that end point (57.3% vs. 33.5% for placebo; $P<0.001$).[1] (*Note:* An ACR20 response is defined as a 20% improvement in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein level.)

In December 2021, the FDA approved upadacitinib, a Janus kinase (JAK) inhibitor, for the treatment of patients who have had inadequate response to, or are intolerant of, one or more tumor necrosis factor-α (TNF) inhibitors.

Dr. Orbai addressed the FDA boxed warning for JAK inhibitors. This warning notes an increased risk for serious infections, mortality, malignancy, major adverse cardiac events and thrombosis. However, similar to risankizumab, upadacitinib proved beneficial in treating patients naive to biologics or with prior biologic use. Also, data indicate that upadacitinib may slow the radiographic progression of PsA, which is important to prevent joint deformities and impaired function in patients.

Next, Dr. Orbai discussed the CONTROL strategy trial.[2] This trial compared the initiation of adalimumab with increased dosing of methotrexate in patients with PsA for whom 15 mg of methotrexate weekly had proved inadequate.

In the study's initial part, patients on 15 mg of methotrexate per week were randomized to either add 40 mg of adalimumab every other week to their regimen or to have their dose of methotrexate increased to 20–25 mg per week.

In the second phase of the trial, patients in the adalimumab plus methotrexate group who responded to this combination discontinued methotrexate. Patients in this group who did not respond had adalimumab increased to 40 mg per week. In the methotrexate monotherapy group, patients who responded to the increased dosing continued methotrexate monotherapy, and patients who did not respond were transitioned to the addition of 40 mg of adalimumab every other week.

The results: Several findings are of note. First, more patients for whom 15 mg of methotrexate weekly proved inadequate achieved minimal disease activity at week 16 with the addition of adalimumab than with methotrexate dose escalation (40% vs. 13%). Among adalimumab responders, the withdrawal of methotrexate still allowed 80% of patients to maintain minimal disease activity through week 32. Among the patients who responded to the increase in methotrexate dosing, continuation of methotrexate kept 67% in minimal disease activity through week 32.

Also, Dr. Orbai pointed out that escalation of methotrexate dosing did not lead to minimal disease activity for most patients. However, the addition of adalimumab for these patients may help, indicating it's often not too late to add a TNF inhibitor. She also said switching from biweekly to weekly adalimumab is helpful for only about 30% of patients. Thus, transitioning to a different medication is likely more appropriate.

Regarding consequences of long-term PsA, conflicting evidence exists as to whether PsA is associated with an increased risk of all-cause mortality compared with the general population. However, a clear association exists between cardiovascular disease and psoriasis. With this finding in mind, joint guidelines from the American Academy of Dermatology and the National Psoriasis Foundation indicate the risk for cardiovascular disease should be multiplied by 1.5 when using a risk calculator if the patient has psoriasis with at least 10% body surface area involvement or qualifies for systemic therapy or phototherapy. These guidelines also recommend screening for comorbidities, such as diabetes, hypertension and hyperlipidemia.

Dr. Orbai noted that TNF inhibitor therapy may be protective against cardiovascular disease in patients with PsA, but management of cardiovascular risk factors remains essential for all patients.[3,4]

Other Options

An important point in the discussion related to the potential to decrease PsA disease activity by reducing the burden of metabolic syndrome through diet, exercise and appropriate medications. Given these approaches, increasing immunosuppression for patients with PsA and ongoing disease activity may not always be the answer. Rather, managing such conditions as diabetes, hypertension, hyperlipidemia and obesity, and working together with the patient, primary care physician and cardiologist, when needed, may help a great deal.

PsA Subtypes

Dr. Orbai concluded by discussing ways to classify the subtypes of PsA. In a study conducted by Eder et al., ultrasound imaging and gene expression clustering were used to identify subtypes of patients with PsA based on location of inflammation (i.e., synovitis-predominant disease, enthesitis-predominant disease and peritendonitis-predominant disease). Among these groups, patients with peritendonitis-predominant disease had the most active overall disease, and it appeared more men than women were in this group.[5] This study provides interesting insights into better understanding the heterogeneity of PsA and more work is needed on this subject. R

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.

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A Vessel for Knowledge

The latest research & management updates for vasculitis

■ BY JASON LIEBOWITZ, MD

BALTIMORE—Many rheumatologists know that vasculitis can rapidly lead to morbidity and mortality for afflicted patients. Thus, understanding the advances in care for vasculitis is key to preventing patient suffering and saving lives.

At the 18th Annual Advances in the Diagnosis & Treatment of the Rheumatic Diseases, held May 13–14 at Johns Hopkins School of Medicine, Baltimore, Brendan Antiochos, MD, assistant professor of medicine, Division of Rheumatology, Johns Hopkins School of Medicine, and assistant director of the Johns Hopkins Vasculitis Center, discussed important topics in vasculitis. He addressed new medications for anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and giant cell arteritis (GCA), tapering of glucocorticoids in patients with vasculitis and issues related to vaccination against SARS-CoV-2 in patients with vasculitis, particularly those receiving B cell-depleting therapy.

Avacopan

Dr. Antiochos began by discussing the ADVOCATE trial, a large, international, randomized clinical trial comparing avacopan (a C5a receptor inhibitor) with prednisone in patients with ANCA-associated vasculitis who were receiving either cyclophosphamide plus azathioprine, or rituximab.[1]

Dr. Antiochos explained that the C5a receptor can be found on myeloid cells and that activation of this receptor helps recruit these cells to sites of injury or inflammation. Avacopan is designed to block the C5a receptor and prevent such recruitment without affecting the formation of the membrane attack complex, which is a product of the complement system and helps protect against certain pathogens.

In 2014, researchers tested a mouse model of necrotizing and crescentic glomerulonephritis mediated by anti-myeloperoxidase antibodies, as would be seen in ANCA-associated vasculitis. They found oral administration of avacopan—called CCX168 at that time—prevented anti-myeloperoxidase-induced necrotizing and crescentic glomerulonephritis in mice expressing human C5aR/CD88.[2]

In the ADVOCATE trial, patients were randomized to receive either 30 mg of avacopan twice daily or an oral prednisone taper, with background therapy of either cyclophosphamide induction followed by azathioprine maintenance or rituximab. The main characteristics of study participants were patients who were newly diagnosed and had seropositive ANCA-associated vasculitis. The majority had renal disease and had been treated with rituximab. The study's primary end points were clinical remission at week 26, with a Birmingham Vasculitis Activity Score (BVAS) of 0 and no steroids for at least four weeks before week 26, and sustained remission at weeks 26 and 52, with no glucocorticoids for at least four weeks before week 52.

The results: Avacopan proved noninferior to the oral prednisone taper for clinical remission at week 26 and was superior to the oral prednisone taper for sustained remission at week 52. Roughly 10% of the avacopan patients experienced a relapse of disease at week 52 compared with about 20% of those in the oral prednisone taper group. In total, patients in the avacopan group received about one-third less total prednisone than those in the oral prednisone taper group. An additional exciting finding described by Dr. Antiochos was that renal function in patients treated with avacopan continued to improve throughout the study.[1]

Dr. Antiochos pointed out that patients treated with rituximab in the study were given this medication only as induction—a dose of 375 mg per meter squared of body surface area, given weekly for four weeks. No maintenance dosing was given at six months after induction, potentially increasing the risk of relapse. Also, the glucocorticoid taper was rapid, with tapering completed by week 21, faster than in current clinical practice. Finally, Dr. Antiochos explained that patients in the avacopan arm of the trial received some glucocorticoids. Thus, this study was not truly a glucocorticoid-free intervention.

Nevertheless, the findings of the ADVOCATE trial and the approval of avacopan by the U.S. Food & Drug Administration (FDA) are notable developments and warrant further exploration of the appropriate use of this medication in clinical practice.

Managing GCA

Next, Dr. Antiochos discussed mavrilimumab and GCA. Mavrilimumab is a human monoclonal antibody that inhibits the human granulocyte macrophage colony-stimulating factor receptor (GM-CSF), which promotes the differentiation, activation and survival of myeloid cells. Because upregulation of GM-CSF and its receptor have been found in temporal artery biopsies in patients with GCA, biologic plausibility exists for the use of mavrilimumab to treat GCA.[3]

In a phase 2, randomized, double-blind, placebo-controlled clinical trial on the efficacy and safety of mavrilimumab, patients with GCA, aged 50–85 and new or relapsing active disease were randomized to receive either mavrilimumab or placebo. Both groups received background treatment with a 26-week prednisone taper. The primary end point of this study was time to first disease flare as defined by erythrocyte sedimentation rate (ESR) levels of >30 mm/hr or C-reactive protein (CRP) levels of >1 mg/dL, along with clinical signs and symptoms of vasculitis activity or imaging evidence of vasculitis activity.

Results: Mavrilimumab proved superior to placebo for time to flare by week 26 and sustained remission in patients with GCA who were treated with a background, 26-week prednisone taper. The medication also appeared safe, with few reported adverse events overall. Dr. Antiochos noted that patients who experienced a disease flare with mavrilimumab demonstrated elevated acute phase reactants. This finding contrasts with what is seen in patients with GCA who are treated with tocilizumab, which suppresses inflammatory markers, such as CRP, making it challenging to use such markers to evaluate if a patient is experiencing disease relapse.

Next, Dr. Antiochos addressed the GUSTO study, a proof-of-concept trial evaluating what happens to patients treated with intravenous pulse steroids at the onset of disease and then with tocilizumab monotherapy without ongoing steroids. Enrolled patients had new-onset disease (i.e., diagnosis within four weeks or less) with CRP levels of >25 mg/L, diagnosis proved with biopsy or magnetic resonance/positron emission tomography imaging, and glucocorticoids given for less than 10 days at a maximum dose of 60 mg of prednisone daily. In the study, patients were treated with 500 mg of intravenous (IV) methylprednisolone daily for three days, one dose of IV tocilizumab measured at 8 mg/kg of body weight, and then 162 mg of subcutaneous tocilizumab given weekly for 52 weeks.

The findings: Patients did better than expected. Although only 25% of patients were in remission after 31 days, 78% were in remission by week 24, with 72% remaining relapse free through week 52. However, one patient suffered the onset of anterior ischemic optic neuropathy, one of the most feared complications of disease due to its effects on vision.[4] Thus, Dr. Antiochos said his takeaway from this proof-of-concept study was that the glucocorticoid course used in this trial was likely too short, but that current tapering protocols used in clinical practice may represent overtreatment.

COVID-19

Lastly, Dr. Antiochos discussed several clinical pearls related to preventing COVID-19 in patients with vasculitis who are receiving, or will receive, therapy with B cell-depleting agents, such as rituximab.

Given the data on this subject, he advised the administration of SARS-CoV-2 vaccine booster shots be scheduled when B cells have reconstituted in patients treated with rituximab. Also, two patients with ANCA-associated vasculitis who, despite complete B cell depletion after treatment with rituximab, reportedly demonstrated an antibody response to a booster vaccination. These two patients received Johnson & Johnson as their initial vaccine and subsequently the Moderna or Pfizer booster series, perhaps demonstrating improved immunogenicity with combining different types of vaccines.[5]

Finally, Dr. Antiochos reminded the audience that in December 2021 the FDA issued an emergency use authorization for Evusheld (tixagevimab and cilgavimab). This authorization is for pre-exposure prophylaxis of individuals who are moderately to severely immunocompromised due to a disease or medication and may not mount an adequate immune response to COVID-19 vaccination. **R**

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.

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2. Xiao H, Dairaghi DJ, Powers JP, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol*. 2014 Feb;25(2):225–231.
3. Corbera-Bellalta M, Alba-Rovira R, Muralidharan S, et al. Blocking GM-CSF receptor α with mavrilimumab reduces infiltrating cells, pro-inflammatory markers and neoangiogenesis in ex vivo cultured arteries from patients with giant cell arteritis. *Ann Rheum Dis*. 2022 Apr;81(4):524–536.
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5. Kant S, Azar A, Geetha D. Antibody response to COVID-19 booster vaccine in rituximab-treated patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int*. 2022 Feb;101(2):414–415.

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THE CIMZIA DIFFERENCE

The Only Biologic with 3-year data *exclusive to nr-axSpA*[1]

I CAN FEEL THE DIFFERENCE

In the C-axSpAnd double-blind period, the primary end point of ASDAS-MI at Week 52 was achieved by 47% of CIMZIA + NBBM-treated patients, compared with 7% of placebo + NBBM-treated patients.[2]* At the end of the SFE (Week 156), ASDAS-MI was achieved by 37% of patients by NRI analysis; using OC analysis, ASDAS-MI was achieved by 46% of patients.[1†]

~70% of patients achieved low disease activity or inactive disease at 1 year and at 3 years[1-5‡]

The ONLY TNFi approved for nr-axSpA

Study Design: C-axSpAnd was a Phase 3, multicenter study investigating the efficacy and safety of CIMZIA in patients with nr-axSpA and objective signs of inflammation. C-axSpAnd consisted of a 1-year, randomized, double-blind, placebo-controlled period (Weeks 0-52) and a 2-year, open-label, SFE (Weeks 52-156). In the double-blind period of C-axSpAnd, 317 subjects ≥18 years of age with adult-onset active axial spondyloarthritis for ≥12 months, but without definitive radiographic evidence of structural damage to sacroiliac joints, were randomized 1:1 to CIMZIA (400 mg loading dose at Weeks 0, 2, and 4, followed by 200 mg Q2W; n=159) or placebo (n=158), which they received in addition to their current NBBM. Patients could make allowed changes to their NBBM or switch to open-label CIMZIA at any time during the study, although changes before Week 12 were discouraged. At Week 52 of the study, patients from both initial treatment groups (including those who had switched to open-label CIMZIA), who completed the double-blind period and consented to entering the SFE (n=243), received open-label CIMZIA 200 mg Q2W (in addition to NBBM) for an additional 104 weeks. Safety and clinical outcome data were analyzed descriptively by initial randomization groups.

*NRI.

†Patients randomized to CIMZIA at baseline and entering the SFE; NRI analysis (n=120), OC analysis (n=95).

‡Comparison of the distribution of CIMZIA-treated patients by ASDAS disease-activity category at baseline, Week 52 (includes only patients who remained on CIMZIA treatment from Week 0 to 52; n=121), and at Week 156 (includes only patients who remained on CIMZIA from Week 0 to 156; n=95). OC analysis.

ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score-Major Improvement; NBBM, non-biologic background medication; nr-axSpA, non-radiographic axial spondyloarthritis; NRI, nonresponder imputation; OC, observed case; Q2W, every two weeks; SFE, safety follow-up extension; TNFi, tumor necrosis factor inhibitor.

cimzia® (certolizumab pegol)

Indication

CIMZIA is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

Important Safety Information

Contraindications

CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylaxis, serum sickness, and urticaria.

Serious and sometimes fatal side effects have been reported with CIMZIA, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens (such as Legionella or Listeria). Patients should be closely monitored for the signs and symptoms of infection during and after treatment with CIMZIA. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member. CIMZIA is not indicated for use in pediatric patients.

Please see the following pages for Important Safety Information and brief summary of full Prescribing Information.

Learn more about the 3-year data

Indication

CIMZIA is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

Important Safety Information

Contraindications

CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylaxis, serum sickness, and urticaria.

Serious Infections

Patients treated with CIMZIA 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.

Discontinue CIMZIA if a patient develops a serious infection or sepsis. Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before CIMZIA use and during therapy. Initiate treatment for latent TB prior to CIMZIA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with CIMZIA prior to initiating therapy in the following patients: with chronic or recurrent infection; who have been exposed to TB; with a history of opportunistic infection; who resided in or traveled in regions where mycoses are endemic; with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start CIMZIA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.

Malignancy

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member. CIMZIA is not indicated for use in pediatric patients.

- Consider the risks and benefits of CIMZIA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among CIMZIA-treated patients compared to control patients.
- In CIMZIA clinical trials, there was an approximately 2-fold higher rate of lymphoma than expected in the general U.S. population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk of lymphoma than the general population.
- Malignancies, some fatal, have been reported among children, adolescents, and young adults being treated with TNF blockers. Approximately half of the cases were lymphoma, while the rest were other types of malignancies, including rare types associated with immunosuppression and malignancies not usually seen in this patient population.
- Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including CIMZIA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis, and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. Carefully assess the risks and benefits of treating with CIMZIA in these patient types.
- Cases of acute and chronic leukemia were reported with TNF blocker use.

Heart Failure

- Worsening and new onset congestive heart failure (CHF) have been reported with TNF blockers. Exercise caution and monitor carefully.

Hypersensitivity

- Angioedema, anaphylaxis, dyspnea, hypotension, rash, serum sickness, and urticaria have been reported following CIMZIA administration. If a serious allergic reaction occurs, stop CIMZIA and institute appropriate therapy. The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex which may cause an allergic reaction in individuals sensitive to latex.

Hepatitis B Virus Reactivation

- Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Test patients for HBV infection before initiating treatment with CIMZIA.
- Exercise caution in patients who are carriers of HBV and monitor them before and during CIMZIA treatment.
- Discontinue CIMZIA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming CIMZIA after HBV treatment.

Neurologic Reactions

- TNF blockers, including CIMZIA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, seizure disorder, optic neuritis, peripheral neuropathy, and Guillain-Barré syndrome.

Hematologic Reactions

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with CIMZIA.
- Consider stopping CIMZIA if significant hematologic abnormalities occur.

Drug Interactions

- Do not use CIMZIA in combination with other biological DMARDS.

Autoimmunity

- Treatment with CIMZIA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

Immunizations

- Patients on CIMZIA should not receive live or live-attenuated vaccines.

Adverse Reactions

- The most common adverse reactions in CIMZIA clinical trials (≥8%) were upper respiratory infections (18%), rash (9%), and urinary tract infections (8%).

Please see the following pages for brief summary of full Prescribing Information.

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PROFESSIONAL BRIEF SUMMARY—CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

CIMZIA® (certolizumab pegol)

WARNINGS:

SERIOUS INFECTIONS

Patients treated with CIMZIA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens including Legionella and Listeria.**

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

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member *[see Warnings and Precautions]*. CIMZIA is not indicated for use in pediatric patients.

INDICATIONS AND USAGE

CIMZIA is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. CIMZIA is indicated for the treatment of adults with moderately to severly active rheumatoid arthritis (RA). CIMZIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA). CIMZIA is indicated for the treatment of adults with active ankylosing spondylitis (AS). CIMZIA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy. CIMZIA is indicated for adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation.

CONTRAINDICATIONS

CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylaxis, serum sickness, and urticaria *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Risk of Serious Infections *(see also Boxed Warning)*

Patients treated with CIMZIA are at an increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (e.g. corticosteroids or methotrexate) may be at a greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis
- with underlying conditions that may predispose them to infection

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMZIA, including patients who have previously or concomitantly received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating CIMZIA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating CIMZIA, assess if treatment for latent tuberculosis is needed; and consider an induration of 5 mm or greater a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of CIMZIA 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 having risk factors for tuberculosis infection. Despite previous or concomitant treatment for latent tuberculosis, cases of active tuberculosis have occurred in patients treated with CIMZIA. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with CIMZIA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision of whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in patients who develop a new infection during CIMZIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with CIMZIA.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with CIMZIA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection.

When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and risks of antifungal therapy.

Malignancies

In the controlled portions of clinical studies of some TNF blockers, more cases of malignancies have been observed among patients receiving TNF blockers compared to control patients. During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.5 (0.4, 0.7) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.1, 1.7) per 100 patient-years among 1,319 placebo-treated patients. During CIMZIA studies of psoriasis, malignancies (excluding non-melanoma skin cancer) were observed corresponding to an incidence rate of 0.5 (0.2, 1.0) per 100 subject-years among a total of 995 subjects who received CIMZIA. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which CIMZIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports. CIMZIA is not indicated for use in pediatric patients.

In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 CIMZIA-treated patients and one case of Hodgkin's lymphoma among 1,319 placebo-treated patients.

In the CIMZIA RA clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. In the CIMZIA PsO clinical trials (placebo-controlled and open label) there was one case of Hodgkin's lymphoma.

Rates in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. Patients with Crohn's disease that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF blocker therapy *[see Adverse Reactions]*. The potential role of TNF blocker therapy in the development of malignancies in adults is not known.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk of using a TNF blocker in combination with azathioprine or 6-MP should be carefully considered.

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blockers, including CIMZIA. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including CIMZIA. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in patients with CHF with another TNF blocker, worsening congestive heart failure (CHF) and increased mortality due to CHF

were observed. Exercise caution in patients with heart failure and monitor them carefully *[see Adverse Reactions]*.

Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, anaphylaxis, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed *[see Adverse Reactions]*. The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex which may cause an allergic reaction in individuals sensitive to latex.

Hepatitis B Virus Reactivation

Use of TNF blockers, including CIMZIA, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.Test patients for HBV infection before initiating treatment with CIMZIA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with CIMZIA should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

Neurologic Reactions

Use of TNF blockers, of which CIMZIA is a member, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and with peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA *[see Adverse Reactions]*.

Hematological Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with CIMZIA *[see Adverse Reactions]*. The causal relationship of these events to CIMZIA remains unclear.

Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

Use with Biological Disease-Modifying Antirheumatic Drugs (Biological DMARDs)

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, etanercept, with no added benefit compared to etanercept alone. A higher risk of serious infections was also observed in combination use of TNF blockers with abatacept and rituximab. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the use of CIMZIA in this combination. Therefore, the use of CIMZIA in combination with other biological DMARDs is not recommended *[see Drug Interactions]*.

Autoimmunity

Treatment with CIMZIA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with CIMZIA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

Patients treated with CIMZIA may receive vaccinations, except for live or live attenuated vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA.

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in antibody response to vaccine between CIMZIA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CIMZIA. Similar proportions of patients developed protective levels of anti-vaccine antibodies between CIMZIA and placebo treatment groups; however, patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared with patients receiving CIMZIA alone. The clinical significance of this is unknown.

Immunosuppression

Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blockers, including CIMZIA, to affect host defenses against infections and malignancies. The impact of treatment with CIMZIA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood *[see Warnings and Precautions and Adverse Reactions]*. The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

ADVERSE REACTIONS

The most serious adverse reactions were:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*
- 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.

In premarketing controlled trials of all patient populations combined the most common adverse reactions (≥ 8%) were upper respiratory infections (18%), rash (9%) and urinary tract infections (8%).

Adverse Reactions Most Commonly Leading to Discontinuation of Treatment in Premarketing Controlled Trials

The proportion of patients with Crohn's disease who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA and 7% for placebo. The most common adverse reactions leading to the discontinuation of CIMZIA (for at least 2 patients and with a higher incidence than placebo) were abdominal pain (0.4% CIMZIA, 0.2% placebo), diarrhea (0.4% CIMZIA, 0% placebo), and intestinal obstruction (0.4% CIMZIA, 0% placebo).

The proportion of patients with rheumatoid arthritis who discontinued treatment due to adverse reactions in the controlled clinical studies was 5% for CIMZIA and 2.5% for placebo. The most common adverse reactions leading to discontinuation of CIMZIA were tuberculosis infections (0.5%); and pyrexia, urticaria, pneumonia, and rash (0.3%).

Controlled Studies with Crohn's Disease

The data described below reflect exposure to CIMZIA at 400 mg subcutaneous dosing in studies of patients with Crohn's disease. In the safety population in controlled studies, a total of 620 patients with Crohn's disease received CIMZIA at a dose of 400 mg, and 614 subjects received placebo (including subjects randomized to placebo in Study CD2 following open label dosing of CIMZIA at Weeks 0, 2, 4). In controlled and uncontrolled studies, 1,564 patients received CIMZIA at some dose level, of whom 1,350 patients received 400 mg CIMZIA. Approximately 55% of subjects were female, 45% were male, and 94% were Caucasian. The majority of patients in the active group were between the ages of 18 and 64.

During controlled clinical studies, the proportion of patients with serious adverse reactions was 10% for CIMZIA and 9% for placebo. The most common adverse reactions (occurring in ≥ 5% of CIMZIA-treated patients, and with a higher incidence compared to placebo) in controlled clinical studies with CIMZIA were upper respiratory infections (e.g. nasopharyngitis, laryngitis, viral infection) in 20% of CIMZIA-treated patients and 13% of placebo-treated patients, urinary tract infections (e.g. bladder infection, bacteriuria, cystitis) in 7% of CIMZIA-treated patients and in 6% of placebo-treated patients, and arthralgia (6% CIMZIA, 4% placebo).

Other Adverse Reactions

The most commonly occurring adverse reactions in controlled trials of Crohn's disease were described above. Other serious or significant adverse reactions reported in controlled and uncontrolled studies in Crohn's disease and other diseases, occurring in patients receiving CIMZIA at doses of 400 mg or other doses include:

Blood and lymphatic system disorders: Anemia, leukopenia, lymphadenopathy, pancytopenia, and thrombophilia.

Cardiac disorders: Angina pectoris, arrhythmias, atrial fibrillation, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, pericarditis, stroke and transient ischemic attack.

Eye disorders: Optic neuritis, retinal hemorrhage, and uveitis.

General disorders and administration site conditions: Bleeding and injection site reactions.

Hepatobiliary disorders: Elevated liver enzymes and hepatitis.

Immune system disorders: Alopecia totalis.

Psychiatric disorders: Anxiety, bipolar disorder, and suicide attempt.

Renal and urinary disorders: Nephrotic syndrome and renal failure.

Reproductive system and breast disorders: Menstrual disorder.

Skin and subcutaneous tissue disorders: Dermatitis, erythema nodosum, and urticaria.

Vascular disorders: Thrombophlebitis, vasculitis.

Controlled Studies with Rheumatoid Arthritis

CIMZIA was studied primarily in placebo-controlled trials and in long-term follow-up studies. The data described below reflect the exposure to CIMZIA in 2,367 RA patients, including 2,030 exposed for at least 6 months, 1,663 exposed for at least one year and 282 for at least 2 years; and 1,774 in adequate and well-controlled studies. In placebo-controlled studies, the population had a median age of 53 years at entry; approximately 80% were females, 93% were Caucasian and all patients were suffering from active rheumatoid arthritis, with a median disease duration of 6.2 years. Most patients received the recommended dose of CIMZIA or higher.

Table 1 summarizes the reactions reported at a rate of at least 3% in patients treated with CIMZIA 200 mg every other week compared to placebo (saline formulation), given concomitantly with methotrexate.

Table 1: Adverse Reactions Reported by ≥3% of Patients Treated with CIMZIA Dosed Every Other Week during Placebo-Controlled Period of Rheumatoid Arthritis Studies, with Concomitant Methotrexate.

Adverse Reaction (Preferred Term)	Placebo+ MTX[#] (%) N =324	CIMZIA 200 mg EOW + MTX (%) N =640
Upper respiratory tract infection	2	6
Headache	4	5
Hypertension	2	5
Nasopharyngitis	1	5
Back pain	1	4
Pyrexia	2	3
Pharyngitis	1	3
Rash	1	3
Acute bronchitis	1	3
Fatigue	2	3

[#]EOW = Every other Week, MTX = Methotrexate.

Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA than in controls. These adverse reactions occurred more frequently among patients with a baseline history of hypertension and among patients receiving concomitant corticosteroids and non-steroidal anti-inflammatory drugs.

Patients receiving CIMZIA 400 mg as monotherapy every 4 weeks in rheumatoid arthritis controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA 200 mg every other week.

Other Adverse Reactions

Other infrequent adverse reactions (occurring in less than 3% of RA patients) were similar to those seen in Crohn's disease patients.

Psoriatic Arthritis Clinical Study

CIMZIA has been studied in 409 patients with psoriatic arthritis (PsA) in a placebo-controlled trial. The safety profile for patients with PsA

treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

Ankylosing Spondylitis Clinical Study
CIMZIA has been studied in 325 patients with axial spondyloarthritis of whom the majority had ankylosing spondylitis (AS) in a placebo-controlled study (AS-1). The safety profile treated with CIMZIA was similar to the safety profile seen in patients with RA.

Non-radiographic Axial Spondyloarthritis Clinical Study
CIMZIA has been studied in 317 patients with non-radiographic axial spondyloarthritis (nr-axSpA-1). The safety profile for patients with nr-axSpA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

Plaque Psoriasis Clinical Studies
In clinical studies, a total of 1112 subjects with plaque psoriasis were treated with CIMZIA. Of these, 779 subjects were exposed for at least 12 months, 551 for 18 months, and 66 for 24 months.

Data from three placebo-controlled studies (Studies PS-1, PS-2, and PS-3) in 1020 subjects (mean age 46 years, 66% males, 94% white) were pooled to evaluate the safety of CIMZIA *[see Clinical Studies (14)]*.

Placebo-Controlled Period (Week 0-16)
In the placebo-controlled period of Studies PS-1, PS-2 and PS-3 in the 400 mg group, adverse events occurred in 63.5% of subjects in the CIMZIA group compared to 61.8% of subjects in the placebo group. The rates of serious adverse events were 4.7% in the CIMZIA group and 4.5% in the placebo group. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the CIMZIA group than in the placebo group.

Table 2: Adverse Reactions Occurring in ≥1% of Subjects in the CIMZIA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Studies PS-1, PS-2, and PS-3.

Adverse Reactions	CIMZIA 400 mg every other week n (%) N=342	CIMZIA 200 mg[5] every other week n (%) N=350	Placebo n (%) N=157
Upper respiratory tract infections[1]	75 (21.9)	68 (19.4)	33 (21.0)
Headache[2]	13 (3.8)	10 (2.9)	4 (2.5)
Injection site reactions[3]	11 (3.2)	6 (1.7)	1 (0.6)
Cough	11 (3.2)	4 (1.1)	3 (1.9)
Herpes infections[4]	5 (1.5)	5 (1.4)	2 (1.3)

1: Upper respiratory tract infection cluster includes upper respiratory tract infection, pharyngitis bacterial, pharyngitis streptococcal, upper respiratory tract infection bacterial, viral upper respiratory tract infection, viral pharyngitis, viral sinusitis, and nasopharyngitis.

2: Headache includes headache and tension headache.

3: Injection site reactions cluster includes injection site reaction, injection site erythema, injection site bruising, injection site discoloration, injection site pain, and injection site swelling.

4: Herpes infections cluster includes oral herpes, herpes dermatitis, herpes zoster, and herpes simplex.

5: Subjects received 400 mg of CIMZIA at Weeks 0, 2, and 4, followed by 200 mg every other week.

Elevated Liver Enzymes
Elevated liver enzymes were reported more frequently in the CIMZIA-treated subjects (4.3% in the 200 mg group and 2.3% in the 400 mg group) than in the placebo-treated subjects (2.5%). Of CIMZIA-treated subjects who had elevation of liver enzymes, two subjects were discontinued from the trial. In controlled Phase 3 studies of CIMZIA in adults with PsO with a controlled period duration ranging from 0 to 16 weeks, AST and/or ALT elevations ≥5 x ULN occurred in 0.9% of CIMZIA 200 mg or CIMZIA 400 mg arms and none in placebo arm.

Psoriasis-Related Adverse Events
In controlled clinical studies in psoriasis, change of plaque psoriasis into a different psoriasis sub-type (including erythrodermic, pustular and guttate), was observed in <1% of CIMZIA treated subjects.

Adverse Reactions of Special Interest Across Indications
Infections
The incidence of infections in controlled studies in Crohn's disease was 38% for CIMZIA-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infections (20% for CIMZIA, 13% for placebo). The incidence of serious infections during the controlled clinical studies was 3% per patient-year for CIMZIA-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis.

The incidence of new cases of infections in controlled clinical studies in rheumatoid arthritis was 0.91 per patient-year for all CIMZIA-treated patients and 0.72 per patient-year for placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, herpes infections, urinary tract infections, and lower respiratory tract infections. In the controlled rheumatoid arthritis studies, there were more new cases of serious infection adverse reactions in the CIMZIA treatment groups, compared to the placebo groups (0.06 per patient-year for all CIMZIA doses vs. 0.02 per patient-year for placebo). Rates of serious infections in the 200 mg every other week dose group were 0.06 per patient-year and in the 400 mg every 4 weeks dose group were 0.04 per patient-year. Serious infections included tuberculosis, pneumonia, cellulitis, and pyelonephritis. In the placebo group, no serious infection occurred in more than one subject. There is no evidence of increased risk of infections with continued exposure over time *[see Warnings and Precautions (5.1)]*.

In controlled clinical studies in psoriasis, the incidence rates of infections were similar in the CIMZIA and placebo groups. The infections consisted primarily of upper respiratory tract infections and viral infections (including herpes infections). Serious adverse events of infection occurred in CIMZIA-treated patients during the placebo-controlled periods of the pivotal studies (pneumonia, abdominal abscess, and hematoma infection) and Phase 2 study (urinary tract infection, gastroenteritis, and disseminated tuberculosis).

Tuberculosis and Opportunistic Infections
In completed and ongoing global clinical studies in all indications including 5,118 CIMZIA-treated patients, the overall rate of tuberculosis is approximately 0.61 per 100 patient-years across all indications.

The majority of cases occurred in countries with high endemic rates of TB. Reports include cases of disseminated (miliary, lymphatic, and peritoneal) as well as pulmonary TB. The median time to onset of TB for all patients exposed to CIMZIA across all indications was 345 days. In the studies with CIMZIA in RA, there were 36 cases of TB among 2,367 exposed patients, including some fatal cases. Rare cases of opportunistic infections have also been reported in these clinical trials. In Phase 2 and Phase 3 studies with CIMZIA in plaque psoriasis, there were 2 cases of TB among 1112 exposed patients *[see Warnings and Precautions]*.

Malignancies
In clinical studies of CIMZIA, the overall incidence rate of malignancies was similar for CIMZIA-treated and control patients. For some TNF blockers, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients *[see Warnings and Precautions]*.

Heart Failure
In placebo-controlled and open-label studies, cases of new or worsening heart failure have been reported for CIMZIA-treated patients. The majority of these cases were mild to moderate and occurred during the first year of exposure *[see Warnings and Precautions]*.

Hypersensitivity Reactions
The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, allergic dermatitis, dizziness (postural), dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, serum sickness, and (vasovagal) syncope *[see Warnings and Precautions]*.

Autoantibodies
In clinical studies in Crohn's disease, 4% of patients treated with CIMZIA and 2% of patients treated with placebo that had negative baseline ANA titers developed positive titers during the studies. One of the 1,564 Crohn's disease patients treated with CIMZIA developed symptoms of a lupus-like syndrome.

In clinical trials of TNF blockers, including CIMZIA, in patients with RA, some patients have developed ANA. Four patients out of 2,367 patients treated with CIMZIA in RA clinical studies developed clinical signs suggestive of a lupus-like syndrome. The impact of long-term treatment with CIMZIA on the development of autoimmune diseases is unknown *[see Warnings and Precautions]*.

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. 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 the incidence of antibodies to certolizumab pegol in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Patients with Crohn's disease were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. In patients continuously exposed to CIMZIA, the overall percentage of patients who were antibody positive to CIMZIA on at least one occasion was 8%; approximately 6% were neutralizing *in vitro*. No apparent correlation of antibody development to adverse events or efficacy was observed. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients not taking immunosuppressants at baseline (3% and 11%, respectively). The following adverse events were reported in Crohn's disease patients who were antibody-positive (N = 100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,242): abdominal pain, arthralgia, edema peripheral, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection.

In two long-term (up to 7 years of exposure), open-label Crohn's disease studies, overall 23% (207/903) of patients developed antibodies against certolizumab pegol on at least one occasion. Of the 207 patients who were antibody positive, 152 (73%) had a persistent reduction of drug plasma concentration, which represents 17% (152/903) of the study population. The data from these two studies do not suggest an association between the development of antibodies and adverse events.

The overall percentage of patients with antibodies to certolizumab pegol detectable on at least one occasion was 7% (105 of 1,509) in the rheumatoid arthritis placebo-controlled trials. Approximately one third (3%, 39 of 1,509) of these patients had antibodies with neutralizing activity *in vitro*. Patients treated with concomitant immunosuppressants (MTX) had a lower rate of antibody development than patients not taking immunosuppressants at baseline. Patients treated with concomitant immunosuppressant therapy (MTX) in RA-I, RA-II, RA-III had a lower rate of neutralizing antibody formation overall than patients treated with CIMZIA monotherapy in RA-IV (2% vs. 8%). Both the loading dose of 400 mg every other week at Weeks 0, 2 and 4 and concomitant use of MTX were associated with reduced immunogenicity.

Antibody formation was associated with lowered drug plasma concentration and reduced efficacy. In patients receiving the recommended CIMZIA dosage of 200 mg every other week with concomitant MTX, the ACR20 response was lower among antibody-positive patients than among antibody-negative patients (Study RA-I, 48% versus 60%; Study RA-II 35% versus 59%, respectively). In Study RA-III, too few patients developed antibodies to allow for meaningful analysis of ACR20 response by antibody status. In Study RA-IV (monotherapy), the ACR20 response was 33% versus 56%, antibody-positive versus antibody-negative status, respectively *[see Clinical Pharmacology]*. No association was seen between antibody development and the development of adverse events.

Approximately 8% (22/265) and 19% (54/281) of subjects with psoriasis who received CIMZIA 400 mg every 2 weeks and CIMZIA 200 mg every 2 weeks for 48 weeks, respectively, developed antibodies to certolizumab pegol. Of the subjects who developed antibodies to certolizumab pegol, 45% (27/60) had antibodies that were classified as neutralizing. Antibody formation was associated with lowered drug plasma concentration and reduced efficacy.

A more sensitive and drug tolerant electrochemiluminescence (ECL)-based bridging assay was used for the first time in the nr-axSpA-1 study, resulting in a greater proportion of samples having measurable antibodies to certolizumab pegol and thus a greater incidence of patients being classed as antibody positive. In the placebo-controlled trial in patients with non-radiographic axial spondyloarthritis, after up to 52 weeks of treatment, the overall incidence of patients who were antibody positive to certolizumab pegol was 97% (248/255 patients). Of these antibody positive patients, higher titers were associated with reduced certolizumab pegol plasma levels.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA, or ECL-based bridging assay, and are highly dependent on the sensitivity and specificity of the assay.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of CIMZIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Vascular disorder: systemic vasculitis has been identified during post-approval use of TNF blockers.

Skin: case of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and new or

worsening psoriasis (all sub-types including pustular and palmoplantar, and lichenoid skin reaction) have been identified during post-approval use of TNF blockers.

Immune System Disorders: sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Melanoma, Merkel cell carcinoma (neuroendocrine carcinoma of the skin) *[see Warnings and Precautions]*.

DRUG INTERACTIONS

Use with Anakinra, Abatacept, Rituximab, and Natalizumab

An increased risk of serious infections has been seen in clinical studies of other TNF-blocking agents used in combination with anakinra or abatacept, with no added benefit. Formal drug interaction studies have not been performed with rituximab or natalizumab. Because of the nature of the adverse events seen with these combinations with TNF blocker therapy, similar toxicities may also result from the use of CIMZIA in these combinations. There is not enough information to assess the safety and efficacy of such combination therapy. Therefore, the use of CIMZIA in combination with anakinra, abatacept, rituximab, or natalizumab is not recommended *[see Warnings and Precautions]*.

Live Vaccines

Avoid use of live (including attenuated) vaccines concurrently with CIMZIA *[see Warnings and Precautions]*.

Laboratory Tests

Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated activated partial thromboplastin time (aPTT) assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-Lupus Anticoagulant (LA) test and Standard Target Activated Partial Thromboplastin time (STA-PTT) Automate tests from Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilized silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. Interference with thrombin time (TT) and prothrombin time (PT) assays has not been observed. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. For more information, healthcare providers or patients can contact:

MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS). The OTIS AutoImmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/

Risk Summary

Limited data from the ongoing pregnancy registry on use of CIMZIA in pregnant women are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes. However, certolizumab pegol plasma concentrations obtained from two studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible in most infants at birth, and low in other infants at birth *(see Data)*. There are risks to the mother and fetus associated with active rheumatoid arthritis or Crohn's disease. The theoretical risks of administration of live or live-attenuated vaccines to the infants exposed *in utero* to CIMZIA should be weighed against the benefits of vaccinations *(see Clinical Considerations)*. No adverse developmental effects were observed in animal reproduction studies during which pregnant rats were administered intravenously a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mg every four weeks.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) 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 risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn's disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant. The clinical significance of BLQ or low levels is unknown for *in utero*-exposed infants. Additional data available from one exposed infant suggest that CIMZIA may be eliminated at a slower rate in infants than in adults *(see Data)*. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

A limited number of pregnancies have been reported in the ongoing pregnancy exposure registry. Due to the small number of CIMZIA-exposed pregnancies with known outcomes (n=54), no meaningful comparisons between the exposed group and control groups may be conducted to determine an association with CIMZIA and major birth defects or adverse pregnancy outcomes.

A multicenter clinical study was conducted in 16 women treated with CIMZIA at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks during the third trimester of pregnancy for rheumatological diseases or Crohn's disease. The last dose of CIMZIA was given on average 11 days prior to delivery (range 1 to 27 days). Certolizumab pegol plasma concentrations were measured in samples from mothers and infants using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.96 to 49.4 mcg/mL) were consistent with non-pregnant women's plasma concentrations in Study RA-I *[see Clinical Studies]*. Certolizumab pegol plasma concentrations were not measurable in 13 out of 15 infants at birth. The concentration of certolizumab pegol in one infant was 0.0422 mcg/mL at birth (infant/mother plasma ratio of 0.09%). In a second infant, delivered by emergency Caesarean section, the concentration was 0.485 mcg/mL (infant/mother plasma ratio of 4.49%). At Week 4 and Week 8, all 15 infants had no measurable concentrations. Among 16 exposed infants, one serious adverse reaction was reported in a neonate who was treated empirically with intravenous antibiotics due to an increased white blood cell count; blood cultures were negative. The certolizumab pegol plasma concentrations for this infant were not measurable at birth, Week 4, or Week 8.

In another clinical study conducted in 10 pregnant women with Crohn's disease treated with CIMZIA (400 mg every 4 weeks for every mother), certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood at the day of birth with an assay that can measure concentrations at or above 0.41 mcg/mL. The last dose of CIMZIA was given on average 19 days prior to delivery (range 5 to 42 days). Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.58 mcg/mL in infant blood; and ranged from 1.87 to 59.57 mcg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in mothers suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg/mL over 4 weeks suggesting that certolizumab pegol may be eliminated at a slower rate in infants than adults.

Animal Data

Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on the surface area) and have revealed no evidence of harm to the fetus due to cTN3 PF.

Lactation

Risk Summary

In a multicenter clinical study of 17 lactating women treated with CIMZIA at 200 mg every 2 weeks or 400 mg every 4 weeks, minimal certolizumab pegol concentrations were observed in breast milk. No serious adverse reactions were noted in the 17 infants in the study. There are no data on the effects on milk production. In a separate study, certolizumab pegol concentrations were not detected in the plasma of 9 breastfed infants at 4 weeks post-partum *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CIMZIA and any potential adverse effects on the breastfed infant from CIMZIA or from the underlying maternal condition.

Data

A multicenter clinical study designed to evaluate breast milk was conducted in 17 lactating women who were at least 6 weeks post-partum and had received at least 3 consecutive doses of CIMZIA 200 mg every 2 weeks or 400 mg every 4 weeks for rheumatological disease or Crohn's disease. The effects of certolizumab pegol on milk production were not studied. The concentration of certolizumab pegol in breast milk was not measurable in 77 (56 %) of the 137 samples taken over the dosing periods using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. The median of the estimated average daily infant doses was 0.0035 mg/kg/day (range: 0 to 0.01 mg/kg/day). The percentage of the maternal dose (200 mg CIMZIA dosed once every 2 weeks), that reaches an infant ranged from 0.56% to 4.25% based on samples with measurable certolizumab pegol concentration. No serious adverse reactions were noted in the 17 breastfed infants in the study.

In a separate study, plasma certolizumab pegol concentrations were collected 4 weeks after birth in 9 breastfed infants whose mothers had been currently taking CIMZIA (regardless of being exclusively breastfed or not). Certolizumab pegol in infant plasma was not measurable i.e., below 0.032 mcg/mL.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant *[see Use in Specific Populations)]*.

Geriatric Use

Clinical studies of CIMZIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Population pharmacokinetic analyses of patients enrolled in CIMZIA clinical studies concluded that there was no apparent difference in drug concentration regardless of age. Because there is a higher incidence of infections in the elderly population in general, use caution when treating the elderly with CIMZIA *[see Warnings and Precautions]*.

OVERDOSAGE

The maximum tolerated dose of certolizumab pegol has not been established. Doses of up to 800 mg subcutaneous and 20 mg/kg intravenous have been administered without evidence of dose-limiting toxicities. In cases of overdosage, it is recommended that patients be monitored closely for any adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Risk of Serious Infections

Inform patients that CIMZIA may lower the ability of the immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections. Because caution should be exercised in prescribing CIMZIA to patients with clinically important active infections, advise patients of the importance of informing their health care providers about all aspects of their health *[see Warnings and Precautions]*.

Malignancies

Counsel patients about the possible risk of lymphoma and other malignancies while receiving CIMZIA *[see Warnings and Precautions]*.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report promptly any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever *[see Warnings and Precautions]*.

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe hypersensitivity reactions. Advise latex-sensitive patients that the needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex *[see Warnings and Precautions]*.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy; patients can call 1-877-311-8972 *[see Use in Specific Populations]*.

Preparation and Administration of CIMZIA Using the Prefilled Syringe

Instruct patients and caregivers on how to inject the Prefilled Syringe. Complete instructions are provided in the Instructions for Use packaged in each CIMZIA Prefilled Syringe kit.

Product manufactured by:
UCB, Inc.,1950 Lake Park Drive, Smyrna, GA 30080
US License No. 1736
For more information, go to www.CIMZIA.com or call 1-866-424-6942.

A CLEAR VISION

Understanding the connection between ophthalmology & rheumatic disease

■ BY JASON LIEBOWITZ, MD

BALTIMORE—The eye may be the window to the soul, but in medicine it can also serve as a harbinger of systemic disease. At the 18th Annual Advances in the Diagnosis & Treatment of the Rheumatic Diseases, held May 13–14 at the Johns Hopkins School of Medicine, Baltimore, Meghan Berkenstock, MD, associate professor of ophthalmology, Wilmer Eye Institute, Johns Hopkins School of Medicine, gave a presentation on the connection between rheumatology and ophthalmology.

Dr. Berkenstock discussed three main topics: 1) the association of uveitis with systemic disease, 2) medications and vaccinations that can be associated with the development of uveitis, and 3) when it's appropriate to refer patients to an ophthalmologist.

Uveitis is an umbrella term for intraocular inflammation that can apply to more than 30 different syndromes, explained Dr. Berkenstock. The etiologies of uveitis can be autoimmune, infectious, neoplastic or idiopathic, and one or more chambers of the eye can be affected. Inflammation of the eye is a rare phenomenon because the eye is generally an immune-privileged site.

Rheumatic Disease

In rheumatoid arthritis (RA) and secondary Sjögren's syndrome associated with keratoconjunctivitis sicca, patients may experience eye dryness, foreign-body sensation, photophobia and red eyes. An increased risk for external infections exists secondary to decreased tear turnover and breakdown of surface epithelium, which can lead to painful and recurrent filamentary keratitis.

Treatments for dry eye associated with Sjögren's syndrome include artificial tears, punctal plugs, topical cyclosporine or tacrolimus, lifitegrast, oral pilocarpine, scleral lenses and autologous serum tears. One of the newest treatments approved by the U.S. Food & Drug Administration for the management of dry eyes is varenicline nasal spray, which may be helpful for select patients.

Patients with RA can also develop scleritis or episcleritis, explained Dr. Berkenstock. If a patient develops scleritis associated with peripheral corneal melting (i.e., peripheral ulcerative keratitis), it's particularly important to evaluate for the possibility of underlying RA. For episcleritis in RA, this condition is typically self-limited but can recur, and treatment may involve topical glucocorticoids and topical non-steroidal anti-inflammatory drugs (NSAIDs).

In patients with scleritis, it's important to evaluate for conditions beyond RA, such as HLA-B27-associated spondyloarthritis, Lyme disease, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and sarcoidosis. The treatment of scleritis typically begins with oral non-steroidal anti-inflammatory drugs (NSAIDs) and can escalate to systemic glucocorticoids—up to the equivalent of 1 mg/kg of prednisone daily. If inflammation recurs before tapering to 7.5 mg or less of prednisone daily, then methotrexate, mycophenolate mofetil or tumor necrosis factor-α (TNF) inhibitors, should be considered.

Dr. Berkenstock noted that if scleral perforation or extensive thinning exists and there is a high risk of scleral rupture, surgery may be necessary.

Acute Anterior Uveitis

In ankylosing spondylitis, a strong association with both HLA-B27 positivity and acute anterior uveitis exists. This form of uveitis can recur or become chronic, may present bilaterally or alternate between eyes, and can occur simultaneously with scleritis. The classic presentation of acute anterior uveitis is eye redness, pain, blurred vision and photophobia.

Screening for Lyme disease, sarcoidosis and syphilis in these patients is important, according to Dr. Berkenstock. Also, RA and systemic lupus erythematosus can, rarely, present with acute anterior uveitis. Treatment of this condition includes topical glucocorticoids; posterior sub-tenon injection with triamcinolone acetonide or other medication; and, in cases of chronic anterior uveitis or in patients who do not tolerate local therapy, oral glucocorticoids and immunomodulators may be appropriate.

The prognosis for these patients tends to be good, with the average episode lasting six weeks or less. However, complications, such as cataracts, macular edema, glaucoma, corneal decompensation, hypotony or phthisis, may occur.

Sarcoidosis

In sarcoidosis, the eye is one of the most commonly affected organs, and ocular manifestations can include granulomatous uveitis, inflammatory glaucoma, optic neuropathy or granulomatous infiltration, and lacrimal gland enlargement with sicca syndrome.

In granulomatous uveitis, the patient may present with mutton fat precipitates on the corneal endothelium. This condition usually involves both eyes in a progressive fashion. Patients may also demonstrate periphlebitis, which is common in the peripheral retina, with perivascular sheathing and severe vasculitis associated with extensive perivascular exudates. Patients whose eyes are subject to these changes may experience venous occlusion and neovascularization.

In patients with granulomatous inflammation of the optic nerve, the optic disc may have a characteristic lumpy and white appearance. Fortunately, recovery of vision for patients with granulomatous inflammation of the optic nerve can be rapid and significant if corticosteroids are started in a timely manner. These patients should also undergo neuroimaging to evaluate central nervous system involvement.

Medications Linked to Uveitis

Medications associated with uveitis include TNF inhibitors, bisphosphonates, oral contraceptives, sildenafil, sulfas, rifabutin, quinidine and clomiphene. Fluoroquinolones may also be associated with uveitis.

Various vaccines have also been associated with the development of uveitis, including those for influenza, hepatitis B, measles/mumps/rubella (MMR), diphtheria/pertussis/tetanus (DPT), varicella and the bacille Calmette-Guerin (BCG) vaccine for tuberculosis. Although more data are needed, reports also exist of patients presenting with uveitis after vaccination against COVID-19.[1]

Referrals

With respect to referral to ophthalmology, Dr. Berkenstock noted that ocular immunology specialists see patients with a range of conditions, including Behçet's disease, relapsing polychondritis, systemic vasculitis, multiple sclerosis, temporal arteritis and central nervous system lymphoma. Certainly, in patients with a red, painful eye and a recent infection, particularly syphilis, tuberculosis, varicella zoster, toxocara or toxoplasmosis, expert eye care may be highly beneficial. R

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.

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What's New in SLE

Pathogenesis & novel therapies

■ BY SAMANTHA C. SHAPIRO, MD

DR. DÖRNER

> 'The challenge for us in 2022 is to improve SLE treatment outcomes to prevent damage and mortality. To do this, we need to employ advanced treatment options and treat to target to minimize glucocorticoid burden.'
>
> —Dr. Dörner

EULAR 2022 (VIRTUAL)—The past few years have seen the U.S. Food & Drug Administration approve three new therapies to treat systemic lupus erythematosus (SLE) and/or lupus nephritis. The rheumatology community is rightfully excited about the potential of belimumab, anifrolumab and voclosporin, but what else is new for SLE?

At the European Alliance of Associations for Rheumatology (EULAR) European Congress of Rheumatology 2022, Thomas Dörner, MD, Department of Medicine and Department of Rheumatology and Clinical Immunology, Charité-Berlin University of Medicine, and German Rheumatism Research Center (DRFZ), Berlin, shared updates on SLE pathogenesis and novel therapies.

Where We Are

In recent years, we've seen new SLE management guidelines emerge from many different parts of the world (e.g., Europe, Canada, the U.K., Latin America). All share the same general recommendations: Glucocorticoid treatment should be limited in dose and duration. Antimalarials are strongly recommended for all patients with SLE. For persistently active and/or life-threatening disease, disease-modifying antirheumatic drugs and biologic treatments should be used according to organ manifestation. And comorbidities, such as hypertension, should be actively treated.[1]

We've also seen pushes to define both low disease activity and remission in SLE.[2,3] With better control of disease activity, we hope to delay damage accrual, disability and premature death. We are moving closer than ever to these goals, but we aren't quite there.

In the Toronto Lupus Clinic, between 1971 and 2013, people with SLE lost about 23 years of life compared with controls, and all-cause and cause-specific standardized mortality rates decreased over time.[4] In a 2018 analysis of U.S. Centers for Disease Control and Prevention (CDC) data, SLE remained among the top 10 causes of death among young women, with non-white patients most severely affected.[5]

A longitudinal cohort study published in March 2022 showed that failure to achieve a low lupus disease activity state (LLDAS) and cumulative glucocorticoid doses are significantly associated with morbidity and mortality in SLE. Never achieving LLDAS was associated with a near fivefold risk of death after adjustment for confounders (adjusted mortality rate hazard ratio 4.98 [95% confidence interval 2.07–12.0]; $P<0.001$).[2,6]

"The challenge for us in 2022 is to improve SLE treatment outcomes to prevent damage and mortality," Dr. Dörner said. "To do this, we need to employ advanced treatment options and treat to target to minimize glucocorticoid burden."

Recent Advances in Pathogenesis

Dr. Dörner highlighted a few new insights into SLE pathogenesis, noting that to discuss them all would take far longer than time allotted.

In SLE, a positive feed-forward loop of adaptive and innate immune activation is comprised of two main signatures: the type I interferon (IFN) signature and the B cell/plasma cell/BLyS signature.

"To which extent these two faces are interrelated—and whether they share one common brain—is not yet clear, but it's clear that they're communicating with each other," he said.[7]

For many years, we've also known anti-IFN antibodies can affect the IFN signature in SLE. Anti-type I and II IFN antibodies are found in 27% of SLE patients.[8]

"The important point to take away here is that in about half of the patients with SLE who have anti-IFN antibodies, those antibodies are neutralizing and down-modulate the IFN signature," Dr. Dörner said. "So to what extent do anti-type I IFN antibodies affect the one-third of lupus patients with low IFN signatures? This is the next question to answer."[9]

Promising New Targets

Dr. Dörner highlighted several potential new therapeutic targets in SLE. Antibodies directed against blood dendritic cell antigen 2 (BDCA2), a unique plasmacytoid dendritic cell (pDC)-specific receptor, inhibits but doesn't deplete pDCs. It also reduces the production of type I IFN and other inflammatory mediators.

"There were very promising results from the phase 2 LILAC trial last year. What I found most interesting was the [positive] effect on tender and swollen joints," he said. The drug was also associated with a positive SLE Responder Index (SRI-4) response compared with placebo.[10]

Iberdomide also holds promise in SLE. Ikaros and Aiolos are two key transcription factors in immune cell development and homeostasis that are linked to genetic risk factors for SLE. Iberdomide promotes the proteasomal degradation of Ikaros and Aiolos.

Dr. Dörner said, "Iberdomide shifts the transcriptional program. It reduces B-cell activation and autoantibody production, targets pDCs and reduces the type I IFN signature. And it simultaneously enhances the function of regulatory T cells."

Iberdomide at the highest dose tested met the primary endpoint of SRI-4 clinical response at week 24 in a recent phase 2 study.[11]

"One of the interesting new questions is to what extent 'deeper' tissue depletion or co-targeting of plasma cells in the bone marrow may result in greater efficacy in SLE," Dr. Dörner said.

He mentioned two new targets: CD38 (cluster of differentiation 38), which is expressed by all bone marrow plasma cells, and CD19, which is expressed by only some bone marrow plasma cells.[12]

Investigators have recently made use of both targets in refractory SLE (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] >20). Case reports describing the efficacy of CD19-targeted chimeric antigen receptor (CAR) T cells and daratumumab, a multiple myeloma drug that targets CD38, were published in the New England Journal of Medicine in 2021 and 2020, respectively.[13,14]

Likely Not the Answer

We've seen disappointing trials in SLE, as well. In 2020, phase 3 studies of ustekinumab were discontinued given lack of efficacy.[15] In 2022, phase 3 baricitinib studies were discontinued given discordant results.[16]

Data remain inconclusive regarding the sequential use of belimumab and rituximab: BLISS-BELIEVE was a phase 2, randomized, double-blind, placebo-controlled, superiority trial in which patients received rituximab, followed by belimumab four to eight weeks later. Belimumab after rituximab significantly reduced serum immunoglobulin G anti-double stranded-deoxyribonucleic acid (IgG anti-dsDNA) levels and reduced the risk of severe SLE flare. However, in the follow-up, phase 3 trial (BEAT LUPUS), the primary endpoint was not met because there were no statistically significant improvements in disease control as measured by SLEDAI-2K score.[17,18]

"We're not sure whether the books can be closed yet," Dr. Dörner said.

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A Young Disease

A holistic approach to the treatment of antiphospholipid syndrome

■ **BY SAMANTHA C. SHAPIRO, MD**

EULAR 2022 (VIRTUAL)—Described only about 40 years ago, antiphospholipid syndrome (APS) is a relatively young disease. It wasn't until 2019 that the European Alliance of Associations for Rheumatology (EULAR) published evidence-based recommendations for the management of APS in adults, and the ACR has not yet released clinical practice guidelines.[1] Although progress is being made, we still have a lot of questions to answer regarding best management practices.

At the EULAR 2022, Ricard Cervera, MD, PhD, senior consultant and head, Department of Autoimmune Diseases, Hospital Clinic of Barcelona, Spain, described a holistic approach to the treatment of APS.

Clot Risk

The incidence of first thrombosis depends on multiple factors, such as the antiphospholipid antibody (aPL) profile, which is defined by the aPL type, multiple vs. single aPL positivity, apL titers and the persistence of aPL positivity on repeated measurements.[1] A high-risk aPL profile is defined as the presence—on two or more occasions at least 12 weeks apart—of a lupus anticoagulant, double or triple aPL positivity, or the presence of persistently high aPL titers.

The aPL profile helps determine the risk of thrombotic and obstetric events and informs the aggressiveness of treatment. *Example:* The incidence of events is less than one per 100 patient-years in aPL asymptomatic carriers, but rises to seven per 100 patient-years in patients with systemic lupus erythematosus (SLE) with obstetric APS.[2] The EULAR recommendations for the management of APS in a patient vary based on aPL profile, history of thrombosis or obstetric complication, coexistence of other systemic autoimmune diseases and the presence of traditional cardiovascular risk factors.[1]

Primary Thromboprophylaxis

Is there anything we can do to prevent clots from occurring in the first place? A 2007 randomized controlled trial—the APLASA study—showed no protective benefit of aspirin for primary thromboprophylaxis in asymptomatic aPL-positive individuals. However, a 2014 meta-analysis of 11 studies found asymptomatic aPL-positive patients treated with long-term, low-dose aspirin (75–100 mg daily) had a 50% risk reduction for occurrence of first clot.[3] This finding held true for patients with SLE and obstetrical APS.

EULAR recommends low-dose aspirin for primary thromboprophylaxis in patients who have a high-risk aPL profile, SLE or obstetrical APS. Low-dose aspirin may also be considered for those with lower risk aPL profiles.[1]

Would anticoagulation added to aspirin also help prevent primary thrombosis? In 2014, the ALIWAPAS trial examined low-dose aspirin vs. low-dose aspirin plus low-intensity warfarin (i.e., international normalized ratio [INR] goal of 1.5) for primary thromboprophylaxis in aPL-positive individuals with SLE or obstetric morbidity (i.e., higher risk patients).[4]

"Results were not as expected," said Dr. Cervera. No significant difference was found in the number of thromboses between groups, but patients on combination therapy had more episodes of bleeding.

"At this time, I recommend low-dose aspirin for primary thromboprophylaxis," Dr. Cervera said. "Should a patient have an aspirin allergy, low molecular weight heparin [LMWH] should be considered for high-risk individuals. Smoking and sedentarism should be avoided, and hypertension and hyperlipidemia effectively controlled. Hydroxychloroquine should also be used for clot prevention in SLE [because] studies show a protective benefit."[5]

Secondary Thromboprophylaxis

In 1995, a landmark trial demonstrated the benefit of warfarin with a goal INR of 3 to 4 for secondary prevention of venous clots in APS.[6] Thereafter, similar benefit was confirmed for the currently recommended INR target of 2 to 3, though a higher target may be appropriate for certain patients.[7]

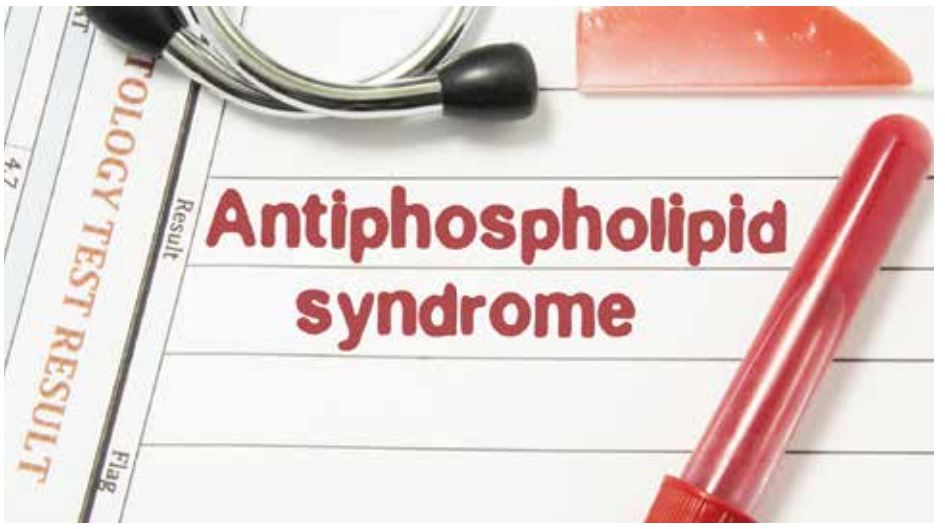
When it comes to arterial clots, the situation may be different. The Euro-Phospholipid Project followed 1,000 patients with APS over 10 years. With the implementation of warfarin, the incidence of venous thrombosis declined over time, but there was still an excess of arterial thrombosis at the 10-year mark.[8]

"This means the therapy we're prescribing to our patients is still not good enough to prevent arterial thrombosis. An INR of 3 to 4 and/or the addition of low-dose aspirin may be the right thing to do in these cases," he said.

Direct Oral Anticoagulants in APS

Warfarin is the cornerstone of secondary thromboprophylaxis in APS, but INR monitoring is taxing on patients and providers alike. What about direct oral anticoagulants?

"We suspected that these may be a good solution, especially for refractory patients," Dr. Cervera said. "Initial mechanistic studies showed promise, but the TRAPS study—the randomized controlled trial comparing rivaroxaban to warfarin in patients with APS—was discontinued early due to an excess of thrombosis in those receiving rivaroxaban."[9]



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The results of the TRAPS study led to warnings from international agencies to avoid the use of direct oral anticoagulants in patients with APS. But the patients studied were high-risk with triple positive aPLs. Dr. Cervera said, "There's some new information and longer follow-up data that suggest it's probably not necessary to avoid [direct oral anticoagulants] in all APS patients. Patients with venous thrombosis only, or only single or double aPL positivity may do okay on these drugs. We are revisiting this question."

CAPS

Catastrophic antiphospholipid syndrome (CAPS) is a highly lethal variant of APS, causing multi-organ failure due to microcirculation thrombosis. The good news is that it's relatively uncommon. According to data from the European Forum on aPL CAPS Registry, only 1% of patients with APS develop CAPS.[10] The CAPS Registry was created in the year 2000 and now includes about 1,000 patients worldwide.

"Initially, the mortality rate from CAPS was 50%," Dr. Cervera said. "So the 50% who recovered—what therapies did they receive? If they received the combination of anticoagulation, steroids and plasma exchange [PLEX] or intravenous immunoglobulin [IVIG], the survival rate was as high as 70%." This finding was a statistically significant difference compared with other treatment combinations.[11]

These data ultimately led to the proposal of triple therapy for CAPS, which includes anticoagulation, high-dose intravenous glucocorticoids and PLEX with or without IVIG.[12,13] Glucocorticoids are included to treat the cytokine storm and systemic inflammatory response that occur in CAPS. PLEX and IVIG help remove the aPL and cytokines from the body as quickly as possible.

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DR. CERVERA

> The EULAR recommendations for the management of APS vary based on the patient's aPL profile, history of thrombosis or obstetric complication, coexistence of other systemic autoimmune diseases & the presence of traditional cardiovascular risk factors.

Antiphospholipid Syndrome *continued from page 51*

"We are very proud to share that with the use of triple therapy, the mortality rate from CAPS has decreased from 75% (if no drugs are used) to 26%. In other words, the risk of death is nearly 10 times higher if you don't use triple therapy. The importance of this cannot be stressed enough," Dr. Cervera said.[14]

Despite the success of triple therapy, some patients with CAPS relapse or don't respond to triple therapy. In these cases, adding rituximab is an option.[15] Because complement is involved in APS pathogenesis, adding eculizumab, a monoclonal antibody targeted against complement C5, may be another option.[16]

Ask the Expert

Dr. Cervera was kind enough to field questions from the audience at the end of his talk.

Question: **What about the risk of thrombosis with IVIG?**

Dr. Cervera: Be aware that [thrombosis] is a potential risk, but it's a small risk as compared with the benefits in this very fatal condition [CAPS].

Question: **What about heparin-induced thrombocytopenia?**

Dr. Cervera: In this case, use fondaparinux.

Question: **Do you discuss the risk of CAPS with all of your patients with APS?**

Dr. Cervera: Patients with triple aPL positivity are at higher risk of developing CAPS, but there are single aPL-positive patients who can get it too. The most important thing is to avoid triggers, such as infection, surgical procedures and lupus flares. Even a simple upper respiratory infection or minor procedure, such as a dental extraction or renal biopsy, can trigger CAPS. Pregnancy can, too. So discuss potential triggers with your patients, and try to prevent those that you can.

Question: **What do you recommend for patients with APS and low platelets?**

Dr. Cervera: Fortunately, thrombocytopenia isn't an issue when treating typical APS because platelets are rarely less than 70,000/μL. But in CAPS, platelet levels can be life-threateningly low. In those cases, first try to increase the platelets with glucocorticoids and IVIG. As soon as platelets are above 10,000–15,000, you can start low-dose heparin prophylaxis. When they reach 40,000 to 50,000, you can start full-dose anticoagulation. 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 also a member of the ACR Insurance Subcommittee.

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What's New in SLE *continued from page 50*

Conclusion

Dr. Dörner concluded his talk on a hopeful note.

"Control of SLE disease activity, glucocorticoid sparing and damage prevention are becoming realistic goals," he said. "Successful translation of SLE key signatures provide the basis for future developments, including restoring immune homeostasis." 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 also a member of the ACR Insurance Subcommittee.

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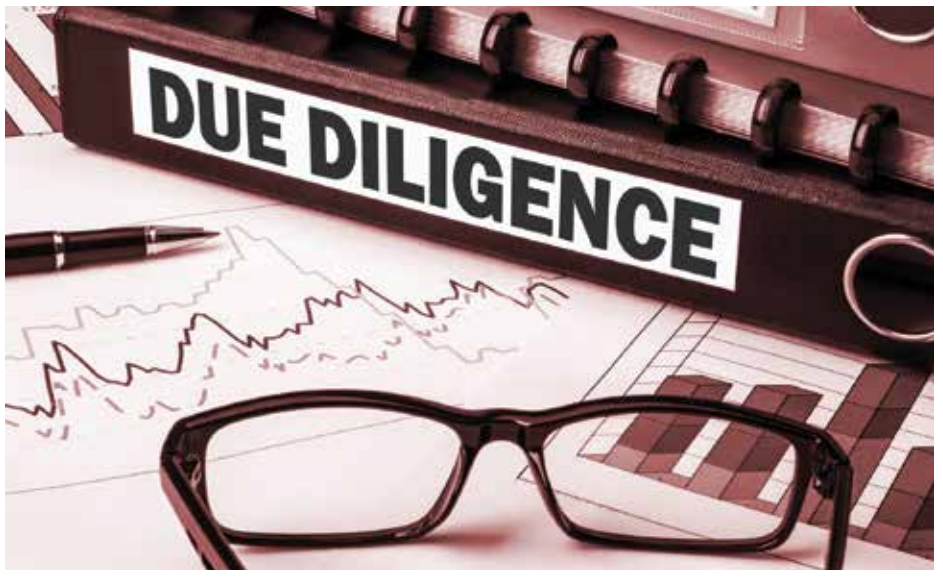
Tackling Due Diligence in Advance of a Sale

Preparation is key to a smooth process

BY EMILY A. JOHNSON, JD



MS. JOHNSON

Healthcare businesses are a hot commodity in the market today. A buyer may even be interested in your healthcare practice right now. Whether or not you've gone down the road of selling your practice before, the process can be stressful and time consuming. A lot of the time and stress centers around one aspect of a transaction—due diligence. Due diligence can certainly feel like a roadblock to both sides of a transaction, but it doesn't have to be.

What Is Due Diligence?

Due diligence is a prospective buyer's opportunity to look under the hood of the business they are interested in purchasing. Once a letter of intent is signed, the buyer will ask for a detailed list of documents and information to evaluate before finalizing the deal. Due diligence can encompass a wide range of information, including financial statements, copies of licenses or permits, corporate formation documents, employee information, policies, procedures, lists of services provided, leases, vendor and payer contracts, asset lists, litigation information and anything else a buyer may need to evaluate the business.

Buyers want to know that the target business is in good working order. As a seller, you want to put your best foot forward to ensure a smooth process. The best time to get your business into shape is well before you go to market, but it can be a real challenge to prepare for questions that have not yet been asked.

A Word of Warning

By not preparing for future due diligence, a seller puts a potential deal at risk. This may be acceptable for some sellers who will go on to find another buyer, but imagine if you *need* to sell the practice. Transactions can be time-sensitive affairs. Buyers will walk away from a deal if they feel a practice's due diligence materials reveal too many issues.

If the buyer in front of you is your best option, you cannot risk the transaction because of a lack of preparation. By turning in inadequate, inscrutable or incorrect records for due diligence requests, you could scare a buyer away—perhaps your best, or only, buyer.

Preparation

With an almost endless number of documents a buyer could request during due diligence, it is difficult to know where to start on preparing your business for an eventual transaction. If you do not have a due diligence request list in front of you, look to other parties that are also evaluating you. If you are being accredited, inspected, audited or surveyed by a third party, use their evaluation process as an opportunity to stress test your practice to see where the gaps are.

Your practice may make perfect sense to you, but in a transaction, it needs to make sense to someone else. So take notes during these third-party interactions. How easy was it for you to assemble the information they asked for? Did you find yourself having to find creative ways to present the information the way they wanted, or was it straightforward? Did the third party need to ask a lot of additional questions to get the answer they needed? At the end of the evaluation, you may receive your updated license or certificate from them, but you also received your marching orders for improvements you can make to ensure any future transactions go smoothly.

When all is said and done with the third-party evaluation, sit down with stakeholders in your practice to discuss how to make the next evaluation better. If certain files were disorganized, create a system that allows you to find the necessary file quickly. If certain information was missing entirely, make a plan to remedy that, and memorialize any changes you make to your processes.

Running a Practice Like It's Always Up for Sale

Maybe your plan is to sell your practice in a couple of years or not until you retire years from now. You may think your practice is doing just fine. Everyone gets their work done, the money comes in and the bills get paid. So why worry about making disruptive changes for a hypothetical sale in the future?

First, due diligence requests often reach several years back. In the healthcare industry, it is not uncommon for information requests to encompass the previous six years because that is the lookback period for many federal healthcare laws. Depending on the structure of the transaction, the buyer may be inheriting issues your practice has had in the past, so they'll want to know everything they're taking on.

The sooner you start the better. For example, if you recently made a change to fix an issue, a diligence request asking for six years of information will still reveal that the fix was not in place for many years.

Second, the actual process of due diligence is expensive. Your lawyers must review your diligence materials for any issues they may need to address with opposing counsel. You and your employees also have to spend valuable time compiling materials for diligence requests. If your records are orderly and accessible, this can significantly decrease the hours spent on these requests. Additionally, if records are kept and presented to buyers in an organized manner, that will result in fewer issues for attorneys to sort through, and fewer additional requests from the buyers.

Finally, by always running your practice like it's up for sale, you create efficiencies, produce better output and hone expertise. Sellers aim to get the best price for their practices and if you build preparation into your culture, you will reap the rewards well before you ever put your practice up for sale.

The prospect of preparing for due diligence can be overwhelming, but you don't have to do it alone. In addition to key stakeholders within your business, involving an attorney can assist with preparation. Attorneys will be able to identify the types of materials that are frequently requested as part of due diligence and can help identify high-risk areas within your specific practice area. Armed with a plan and some partners, you will be well on your way to a successful sale. R

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Deucravacitinib for the Treatment of PsA

Phase 2 study shows promising results

■ **BY MICHELE B. KAUFMAN, PHARMD, BCGP**

EULAR 2022 (VIRTUAL)—Tyrosine kinase 2 (TYK2) is an intracellular kinase in the Janus kinase (JAK) family that mediates the signaling of multiple cytokines, including interleukin (IL) 23, IL-12 and type 1 interferons, which are integral to the immunopathogenesis of psoriatic arthritis (PsA). Deucravacitinib is an oral, selective, intracellular JAK inhibitor that, at therapeutic doses, does not inhibit JAK1, JAK2 or JAK3.[1,2] The agent is currently being evaluated in global clinical trials to treat diseases including PsA, psoriasis, lupus and inflammatory bowel diseases.

In a phase 2 trial, deucravacitinib proved significantly more efficacious for achieving minimal disease activity in patients with active PsA after 16 weeks than placebo. These data were presented by Arthur Kavanaugh, MD, a rheumatologist and professor of medicine at the University of California, San Diego, during the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), June 1–4, Copenhagen, Denmark.

This double-blind, multicenter study (NCT03881059) evaluated the effects of deucravacitinib on individual components of minimal disease activity. Minimal disease activity was defined as achieving five of the seven following criteria:

1. A tender joint count of ≤1;
2. A swollen joint count of ≤1;
3. Tender entheseal points of ≤1;
4. Patient global assessment of disease activity score of ≤20;
5. A patient global assessment of pain score of ≤15;
6. A Health Assessment Questionnaire-Disability Index (HAQ-DI) score of ≤0.5; and
7. A Psoriasis Area and Severity Index [PASI] score of ≤1 or body surface area [BSA] of ≤3%.

The study enrolled 203 patients with a PsA diagnosis of at least six months who fulfilled Classification Criteria for PsA at screening and had active joint disease in at least three tender and swollen joints, high-sensitivity C-reactive protein (CPR) of at least 3 mg/L and at least one plaque psoriasis lesion of at least 2 cm. To participate in the study, patients also had to be either intolerant to or experienced ineffective treatment with at least one non-steroidal anti-inflammatory drug (NSAID), one conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) and/or one tumor necrosis factor (TNF) inhibitor.

Patients were randomized in a 1:1:1 ratio to receive either 6 mg of deucravacitinib once daily, 12 mg of deucravacitinib once daily or placebo. The percentage of patients who achieved minimal disease activity and the proportion of patients who achieved each component of minimal disease activity, minimal disease activity responders and nonresponders were assessed through week 16.

The Results

Of the 203 initial patients, 180 completed the 16-week study, including 88% of the placebo group (n=58 of 66 patients), 90% of the 6 mg of deucravacitinib group (n=63 of 70 patients) and 88% of the 12 mg of deucravacitinib group (n=59 of 67 patients). The patient demographics and baseline disease characteristics were relatively similar across all three groups.

At baseline, no patient met five of the seven criteria required to be classified as having minimal disease activity. However, several of the individual components of minimal disease activity were achieved. *Example:* The criteria for tender entheseal points of ≤1 was met by 57.6% of patients who received placebo, 64.3% of patients who received 6 mg of deucravacitinib and 65.7% of patients who received 12 mg of deucravacitinib.

> In a phase 2 trial, deucravacitinib proved significantly more efficacious for achieving minimal disease activity in patients with active PsA after 16 weeks than placebo.

At week 16, 7.6% of patients who received placebo, 22.9% of patients who received 6 mg of deucravacitinib and 23.9% of patients who received 12 mg of deucravacitinib achieved minimal disease activity. Deucravacitinib treatment compared with placebo treatment led to a numerically greater mean reduction in all minimal disease activity components compared with baseline. Additionally, at week 16, more patients treated with deucravacitinib achieved the threshold levels for each minimal disease activity component than patients who received placebo.

This study showed that patients treated for 16 weeks with deucravacitinib achieved higher rates of minimal disease activity than patients who received placebo. This agent is on its way to proving its effectiveness for managing patients with PsA and other immune-mediated diseases. It may soon be added to the armamentarium for these disorders. **R**

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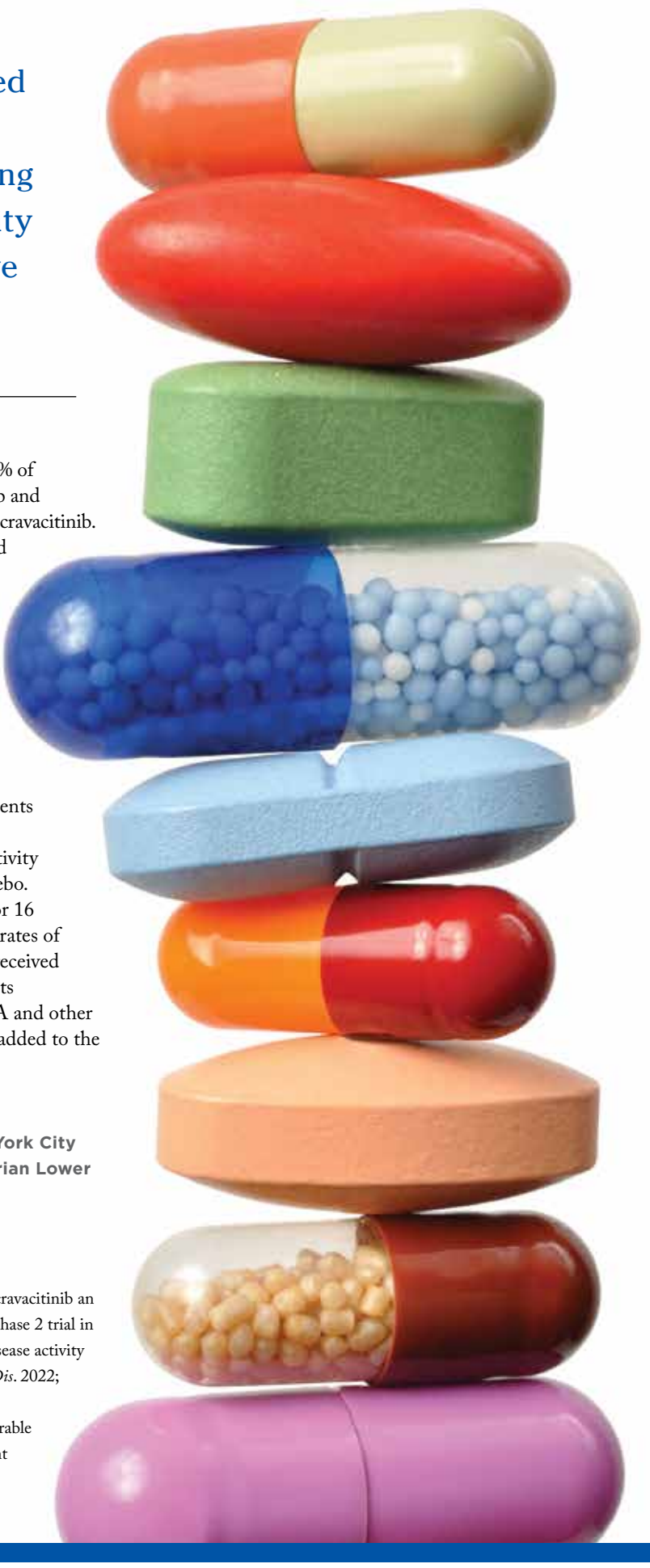

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Dr. Glenn Parris: Novelist

Rheumatologist combines his love of medicine with writing

BY LINDA CHILDERS


Dr. Parris

'The more I wrote, the more I learned that every draft didn't have to be perfect. It was more important to just keep writing.'
—Dr. Parris

Sometimes, late at night, after his wife Carla has gone to bed, Glenn Parris, MD, rheumatologist, founder and CEO of Parris and Associates Rheumatology, Lawrenceville, Ga., sneaks into his home office to continue working on one of his novels.

"My wife thinks I'm asleep, but I use the time to compose my thoughts and write a couple of chapters," Dr. Parris says. "I try to write for a couple of hours every weekend, and also in airports and hotel rooms when I'm traveling."

A Story Begins

Dr. Parris' love for the written word began when he was a young boy growing up in New York City. An avid reader who spent hours devouring science fiction novels, he counts Isaac Azimov, Frank Herbert, Octavia Butler and Larry Niven among his favorite authors. His passion for the written word grew over the years to include a love of writing.

While completing his fellowship at Emory University School of Medicine in Atlanta, Dr. Parris began writing stories based on the genres he enjoyed reading the most, including science fiction, fantasy and suspense/thriller mysteries.

"At the time, I was writing for pleasure," Dr. Parris says. "The more I wrote, the more I learned that every draft didn't have to be perfect. It was more important to just keep writing."

Write What You Know

After moving cross-country from Buffalo, N.Y., to complete his medical residency and rheumatology fellowship at Emory University, Dr. Parris fell in love with the Atlanta suburbs. He put his writing on hold as he proceeded to get married, have two children and build a burgeoning rheumatology practice.

It wasn't until 2010 that Dr. Parris began to contemplate publishing a novel when his wife gave him a gift, enrolling him in a writing workshop for doctors led by novelists and retired physicians Tess Gerritsen and the late Michael Palmer.

Aspiring writers often hear the phrase, "Write what you know," and as he penned his first book, *The Renaissance of Aspirin*, a Jack Wheaton Mystery Doc novel, published in 2013, Dr. Parris found his scientific outlook influenced his writing.

"The story is a medical mystery based in Atlanta that centers around two young doctors who unwittingly possess a cure for fibromyalgia," Dr. Parris says. "The idea for this book was conceived in part because of my frustration that we haven't made the same strides with understanding and treating fibromyalgia as we have with rheumatoid arthritis and other inflammatory diseases."

His first book received positive reviews from readers who praised his "unique blend of deft storytelling and medical know-how." In 2017, Dr. Parris published a novella, *Unbitten: A Vampire Dream*, followed by his second novel, *Dragon's Heir: The Archeologist's Tale,* in 2018. In *Dragon's Heir*, Dr. Parris takes a turn into the world of science fiction/fantasy, exploring what might have transpired if humanoid dinosaurs returned to Earth only to find it inhabited by humans.

Afrofuturism

Dr. Parris is considered an expert in Afrofuturism, a cultural movement that combines science fiction and fantasy, reflecting the experiences of the African diaspora. One of the most recent examples of Afrofuturism is the *Black Panther* movie, featuring the late actor Chadwick Boseman and based on the popular Marvel comic series set in the fictional kingdom of Wakanda.

When Dr. Parris learned Marvel was publishing an anthology of stories from the African diaspora, titled *Black Panther: Tales of Wakanda*, he submitted a story for consideration. The anthology, released in 2021, includes Dr. Parris' story, *The Underside of Darkness*.

"My earliest memories of reading science fiction began with comic books when I was around 8 years old," Dr. Parris says. "I had a preference for Marvel comics because they had a more intriguing story structure."

Dr. Parris' most recent novel, *Dragon's Heir* (*The Efilu Legacy*), a blend of science fiction and fantasy, was published in May 2022.

"When I write, I like to cast the characters in my head as if I were casting a movie," he says. "I want them to be three-dimensional and relatable to readers."

Dr. Parris is currently working on a sequel to *The Renaissance of Aspirin*. He says that over the years, his writing style has matured and it now takes him six months to a year to finish writing a novel.

"I don't have a degree in literature, so I stumbled a little early on in my writing career," he admits. "The stories were good, but I had an awkward writing style."

He also learned that although he can't be an expert in everything, he can tap into the expertise of others.

"I have a former employee who went to work with the state department, and their vetting process included an interview with me. The person who interviewed me knew I was a writer, which told me that he had investigated my background before he interviewed me. He was very helpful in answering some questions about espionage and told me if I ever needed a consultant for a future novel he would be happy to offer his experience," Dr. Parris says. "That agent was one of the most interesting characters I've ever met.

"When I'm working on developing characters for a new novel, I've found that many of my best ideas come from people watching."

Advice for Aspiring Writers

For other rheumatologists who are aspiring writers, Dr. Parris says his best advice is: "Write the book you want to read."

"Tell the story in your voice, develop your story, and complete your first draft," Dr. Parris says. "When you're done, work on refining your first draft with help from an editor or a writer's critique group."

To learn more about Dr. Parris and his novels, visit **glennparris.com**. R

Linda Childers is a health writer located in the San Francisco Bay Area.

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.

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

Ref: 20071734 Revised: April 2022

LAB-7083 **MASTER**

US-RNQR-220410

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 or 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.

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.** Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2 *Ann Rheum Dis.* 2021;80(3):312-320. **3.** Mease PJ, Lertratanakul A, Papp KA, et al. Upadacitinib in patients with psoriatic arthritis and inadequate response to biologics: 56-week data from the randomized controlled phase 3 SELECT-PsA 2 study. *Rheumatol Ther.* 2021. doi:10.1007/s40744-021-00305-z **4.** Supplement to: McInnes IB, Anderson JK, Magrey M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. *N Engl J Med.* 2021;384(13):1227-1239. doi:10.1056/NEJMoa2022516 **5.** A study in healthy adults and adult subjects with rheumatoid arthritis to evaluate the safety, tolerability, and pharmacokinetics after multiple doses of ABT-494. ClinicalTrials.gov identifier: NCT01741493. Updated November 20, 2017. Accessed February 15, 2022. https://clinicaltrials.gov/ct2/show/NCT01741493 **6.** Cohen SB, van Vollenhoven R, Curtis JR, et al. Integrated safety profile of upadacitinib with up to 4.5 years of exposure in patients with rheumatoid arthritis. Poster presented at: The European Congress of Rheumatology; June 2-5, 2021; E-Congress. **7.** Blauvelt A, Teixeira HD, Simpson EL, at al. Upadacitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: analysis of the Heads Up phase 3 trial. Poster presented at: 11th Georg Rajka International Symposium on Atopic Dermatitis; April 19-20, 2021; hybrid meeting. **8.** A study to evaluate the long-term safety and efficacy of upadacitinib (ABT-494) in participants with ulcerative colitis (UC). ClinicalTrials.gov identifier: NCT03006068. Updated February 1, 2022. Accessed March 8, 2022. https://clinicaltrials.gov/ct2/show/NCT03006068 **9.** Burmester GR, Winthrop K, Blanco R, et al. Safety profile of upadacitinib up to 3 years in patients with psoriatic arthritis: an integrated analysis from the phase 3 program. *Ann Rheum Dis.* 2021;80(suppl 1):1287-1288. doi:10.1136/annrheumdis-2021-eular.395 **10.** Colombel JF, Panaccione R, Nakase H, et al. The safety profile of upadacitinib maintenance therapy in ulcerative colitis in the Phase 3 U-ACHIEVE study is consistent with that in approved indications. Poster presented at: Congress of European Crohn's and Colitis Organisation. February 16-19, 2022; E-Congress. **11.** Data on file, AbbVie Inc. ABVRRTI71865. **12.** Data on file, AbbVie Inc. ABVRRTI73629. **13.** Data on file, AbbVie Inc. RINVOQ_Patients Prescribed_031422. **14.** McInnes IB, Anderson JK, Magrey M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. *N Engl J Med.* 2021;384(13):1227-1239. doi:10.1056/NEJMoa2022516. **15.** Supplement to: Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. *Ann Rheum Dis.* 2021;80(3):312-320. **16.** Data on file, AbbVie Inc. ABVRRTI74110. **17.** Data on file, AbbVie Inc. ABVRRTI74056. **18.** Data on file, AbbVie Inc. April 2022.

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

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For active psoriatic arthritis (PsA) in adult TNFi-IR patients[1]

RINVOQ® upadacitinib

DEFY EXPECTATIONS
CHALLENGE TREATMENT GOALS IN PsA

RINVOQ met its primary endpoint (ACR20 at Week 12) in 2 clinical trials[1,a]

✓ Disease Control[2,3]

Minimal disease activity (MDA)[b] evaluated at Week 24, with results up to ~1 year

✓ Joint Efficacy[1-3]

- ACR20 evaluated at Week 12, with results at Week 2 and up to ~1 year
- ACR50/70 evaluated at Week 12, with results up to ~1 year
- ΔmTSS* and complete resolution of enthesitis (LEI=0) and dactylitis (LDI=0) evaluated at Week 24, with results up to ~1 year

*ΔmTSS was evaluated in non-bDMARD–IR patients.[4] RINVOQ is indicated for TNFi-IR patients.

✓ Skin Clearance[2,3]

PASI 75[c] evaluated at Week 16, with results up to ~1 year

RINVOQ is not indicated for the treatment of plaque psoriasis

✓ Safety Data Across 5 Indications in Rheumatology, Dermatology, and Gastroenterology[1]

- 18 clinical trials, establishing a breadth of experience across RA, PsA, AS, UC, and AD indications[1,6-8†]
- >18,500 patient-years of exposure to RINVOQ 15 mg or 30 mg[6,9-12,16‡]
- >10,500 patients in global clinical trials across US-approved indications[1,6,7,9,12§]
- ~5.5 years max. exposure beginning in RA (~3.5 yrs median) to RINVOQ 15 mg as of 6/30/21[17]

✓ Commitment to Exceptional Access and Patient Support[18]

- >95% preferred[d] commercial and Medicare Part D coverage in PsA[e]
  - National Commercial Formulary coverage under the pharmacy benefit as of May 2022
- 1:1 support to help patients start and stay on track with their prescribed treatment plan

Learn more at **RinvoqHCP.com/PsA**

†Includes SELECT-PsA 1 and SELECT-PsA 2 for PsA; SELECT-EARLY, SELECT-MONOTHERAPY, SELECT-NEXT, SELECT-COMPARE, SELECT-BEYOND, and SELECT-CHOICE for RA; 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.[1,6-9,12]
‡Includes 12,259.5 patient-years in RA trials as of 6/2021, 2504.6 patient-years in PsA trials as of 6/2021, 2787.6 patient-years in AD trials as of 11/2020, 381.1 patient-years in UC trials as of 4/2021, and 577.3 patient-years in AS trials as of 11/2020 for SELECT-AXIS 1 and 8/2021 for SELECT-AXIS 2.[6,8-12,16]
§RA: RINVOQ 15 mg, upadacitinib 30 mg; PsA: RINVOQ 15 mg, upadacitinib 30 mg; AS: RINVOQ 15 mg; AD: RINVOQ 15 mg and 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.[1,6,7,9,10]
‖Based on prescription data with RINVOQ 15 mg in adults with moderate to severe RA as of December 2021.

[a]SELECT-PsA 1 (PsA-I; non-bDMARD–IR, n=1705; 24-week, double-blind, randomized, placebo- and active comparator–controlled) [primary endpoint at Week 12: ACR20 response vs placebo, select ranked secondary endpoints: at Week 24, ΔmTSS vs placebo; data observed for RINVOQ up to 56 weeks (~1 year)]; SELECT-PsA 2 (PsA-II; bDMARD-IR, n=642; 24-week double-blind, randomized, placebo-controlled) [primary endpoint at Week 12: ACR20 response vs placebo, select ranked secondary endpoints: at Week 12, ΔHAQ-DI vs placebo; at Week 16, PASI 75 vs placebo; at Week 24, MDA vs placebo; additional secondary endpoints at Week 12: ACR50/70 response vs placebo; data observed for RINVOQ up to 56 weeks (~1 year)].[1-3,14] [b]MDA is achieved when meeting 5 of 7 criteria: tender joint count ≤1, swollen joint count ≤1, PASI ≤1 or BSA-Psoriasis ≤3%, pain ≤1.5 (0-10 NRS), PtGA disease activity ≤2 (0-10 NRS), HAQ-DI ≤0.5, LEI ≤1.[15] [c]PASI assessed in patients with psoriatic skin involvement of ≥3% BSA at baseline.[2] [d]Preferred coverage means a product is placed on the plan's preferred formulary. Preferred may include the lowest copay or coinsurance tier.[18] [e]Coverage requirements and benefit designs vary by payer and may change over time. Please consult with payers directly for the most current reimbursement policies.

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.

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 next page of this advertisement.

Please see Brief Summary of full Prescribing Information on the next page of this advertisement.

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ACR=American College of Rheumatology; AD=atopic dermatitis; AS=ankylosing spondylitis; bDMARD=biologic DMARD; BSA=body surface area; DMARD=disease-modifying antirheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; IR=intolerance or inadequate response; LDI=Leeds Dactylitis Index; LEI=Leeds Enthesitis Index; mTSS=modified total Sharp score; NRS=numeric rating scale; PASI=Psoriasis Area and Severity Index; PtGA=Patient Global Assessment; RA=rheumatoid arthritis; TNFi=tumor necrosis factor inhibitor; UC=ulcerative colitis.