VOLUME 16 | NUMBER 9 | SEPTEMBER 2022 | WWW.THE-RHEUMATOLOGIST.ORG

THE Rheumatologist®

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

RHEUMINATIONS™

Cliff Diving

Evergreening & other oddities

■ BY PHILIP SEO, MD, MHS

The glassblowers were in revolt. The island of Murano, in the 13th century, was a perfect home for the glassblowing industry. Connected to Venice through a system of bridges, Murano was surrounded by waters that protected the city from the furnaces that fueled the glassblowers' craft. The Republic of Venice dominated trade throughout the Mediterranean, which created a natural market for its wares.[1]

Life was good. Too good.

As the renown of the Venetian glassblowers increased, other cities attempted to woo them away. The most common proffers included debt forgiveness and immunity from the prosecutorial system. Rome had a unique trump card: The papal home was able to offer forgiveness of sins to an adequately gifted artisan who agreed to relocate to the Eternal City.[2]

The Venetian glassblowers' guild was aghast. The guild viewed glassblowing expertise as communal property, not belonging to any one artisan. The idea that any individual glassblower could pack his pipes and take that communal property to another city was anathema. The guild's initial response was predictable: It simply forbade artisans from leaving Venice. Glassblowers who gave away guild secrets

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STRATEGIES & TIPS TO IMPROVE THE ONLINE LEARNING EXPERIENCE

■ BY LAURA E. RAY, MA, MLS, ON BEHALF OF THE ARP E-LEARNING SUBCOMMITTEE OF THE ACR COMMITTEE ON EDUCATION

Developing instructional sessions or courses for delivery in online (i.e., asynchronous, not live) or remote (i.e., synchronous, live) learning environments rests on a foundation of traditional instructional design and active learning concepts. Successful online/remote instruction interprets those foundational concepts through technological and multimedia components. For example, the ADDIE instructional design model may be interpreted:

- Analyze—determine the instructor's readiness, technological infrastructure and resources, the learners' needs and instructional goals;
- Design—based on the analysis, write learning objectives and select digital tools appropriate for the technological infrastructure to meet the instructional goals;
- Develop—create content, activities and assessments with a focus on multimedia and interactive formats;
- Implement—launch the course; and
- Evaluate—beyond assessments, regularly test course components and modify them as needed.[1]

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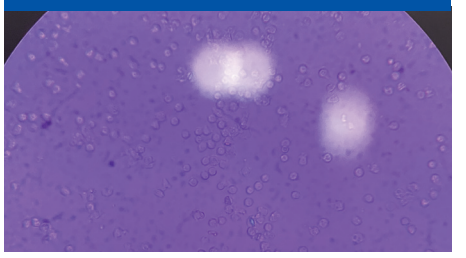
FELLOWS FORUM: CASE



CPPD Presenting as Pseudosepsis

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LOST & FOUND

The Role of Uric Acid in Gout

■ PAGE 22

IMAGE CONTEST

Saddle Nose & Cauliflower Ear Deformities

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EULAR 2022

JAK Inhibitor Update; Prognostication in RA; Difficult-to-Treat RA; Difficult-to-Treat Lupus; Imaging in Gout; Glucocorticoids—How Much Is Too Much?; & More ■ PAGE 34

PROFILE

Anne R. Bass, MD

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American College of Rheumatology
Empowering Rheumatology Professionals

WILEY

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.

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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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were subject to heavy fines and disallowed from returning to Venice to ply their craft.[3]

This worked about as well as you might have expected. Once artisans were outside city limits, the Venetian guild had limited ability to enforce its punishments on the artisans who now fell under the protection of Rome or an equally powerful city. So the guild came up with another incentive: cold hard cash.

Venice realized its riches depended on constant innovation, both in glassblowing and other areas. To entice artisans to bring new skill sets to Venice, the Venetians created the Statute on Industrial Brevets on March 19, 1474, which stated:[4]

> *Any person in this city who makes any new and ingenious contrivance, not made heretofore in our dominion, shall, as soon as it is perfected so that it can be used and exercised, give notice of the same to our office of Provveditori de Comun [State Judicial Office], it being forbidden up to 10 years for any other person in any territory and place of ours to make a contrivance in the form and resemblance thereof, without the consent and license of the author.*

Thus, the modern patent was born.

Since then, the principles underlying the patent have remained surprisingly static: To encourage innovation, the government grants a time-limited monopoly to the innovator. During this period, the innovator alone reaps the rewards of their labors. When the monopoly expires, the information underlying the patent disseminates to spur further innovation.

Previously, time-limited monopolies were granted to innovators on an *ad hoc* basis. The Venetian statute codified the process, making such monopolies available to any inventor, not just the well connected.

Patents *Ad Absurdum*

Prior to World War II, the scientific community largely eschewed drug patents:[5]

> *[M]ost pharmacists and physicians participating in the discovery and study of therapeutic agents have opposed their patenting if not their commercialization. Historians of medicine have accordingly recalled the stands taken by the British Medical Research Council, the American Pharmacological Association, the American Medical Association, or the French Académie de Médecine against patents and more generally against intimate collaborations between medical researchers and the drug industry on the grounds that such connections would result in conflict of interests, threaten the open circulation of knowledge, and hinder public access to therapies essential to life.*

Moral opposition to drug patents waned after World War II, largely due to a drug you may have heard of: penicillin. While Alexander Fleming discovered penicillin in 1928, it was Howard Florey, PhD, who discovered in 1940 how to manufacture enough penicillin to test in humans. Dr. Florey, working with Andrew J. Moyer, PhD, an American scientist in the U.S. Department of Agriculture's North Region Research Laboratories at Peoria, Ill., developed a method to produce penicillin in even larger quantities.[6]

Dr. Florey refused to patent the process, believing it would be immoral to keep this information away from those who might benefit. The American scientist, Dr. Moyer, had no such compunction and was awarded a patent in 1948 that listed him as the sole inventor of the process.[7]

In the U.S., both patent law and U.S. Food & Drug Administration (FDA) law govern the exclusivity rights for new pharmaceutical products. Even without a patent, the FDA will grant a five-year exclusivity period for a new chemical entity (NCE) used in a drug. During these five years, no other company can submit an Abbreviated New Drug Application (ANDA) to the FDA for a drug product containing the NCE. In practice, this five-year period often becomes a six- or seven-year period of exclusivity because it often takes the FDA two or more years to review and approve an ANDA once filed.[8] For biologics, seven years of exclusivity is automatically granted. Additional time is also routinely granted for pediatric and orphan drugs.

Pharmaceutical manufacturers are incentivized to file for patents because they substantially extend the exclusivity period. From the time the patent is granted, the company has exclusive rights to the NCE for 20 years. That said, drug development may take up to 15 years, so by the time the drug comes to market, the patent may be close to expiring. In the pharmaceutical industry, this expiration of patent protection is referred to as falling off the *patent cliff*.

To prevent their drugs from falling off that cliff, companies often seek to extend the exclusivity period for a drug by filing secondary patents in a process called *evergreening*.[9]

Evergreening involves making small changes to branded drugs that may not confer a therapeutic benefit. Such changes may include route of administration, dosage—even the color of the pill. Other changes may involve the production and manufacturing process or finding new indications for old drugs. All of these can serve as justification for a secondary patent to extend the patent protection for a drug, rendering it evergreen.

Some companies have looked for more creative ways to preserve their patents. A *patent thicket* is created by obtaining multiple patents that cover different aspects of the technology needed to manufacture a drug, all of which would need to be challenged by a potential competitor.[10] Another approach was developed by Allergan, which transferred all patents for its eye drug, Restasis, to the St. Regis Mohawk Tribe because it holds sovereign immunity against intellectual property lawsuits.

The U.S. Supreme Court eventually closed this loophole. In fact, the court system would likely invalidate many of the improvidentially granted patents and other end runs used by companies to preserve exclusivity. The problem, of course, is that taking a company to court over a patent takes time and money that many generic and biosimilar manufacturers don't have. For many competitors, a thick patent thicket provides a powerful disincentive against challenging a blockbuster drug patent.

The results of these strategies are exactly what you would expect:[11]

- Over 70% of the 100 best-selling drugs between 2005 and 2015 had their protection extended at least once and almost 50% received more than one exclusivity extension;
- The 12 best-selling drugs in the U.S. in 2017 had an average of 125 patent applications, providing them with an average of 38 years of exclusivity, which is almost twice the 20-year original patent protection;
- Humira was approved by the FDA in 2003. Thanks to 247 patent filings, AbbVie has exclusive rights to market adalimumab until 2034, although it has brokered deals with individual companies to bring biosimilar agents to market in 2023. The price of Humira increased by 18% every year between 2012 and 2016;
- Revlimid was approved by the FDA in 2005. It has a patent thicket of 96 patents that potentially provide 40 years of competition-free profit; and
- Lantus was approved by the FDA in 2000. A patent thicket of 49 patents may prevent a generic form of Lantus from entering the market for 37 years.

Who suffers as a result of evergreening? We do. One year after a generic drug enters the market, the price of the drug drops by more than 60% on average. Substituting biosimilars for bio-originators could save the U.S. healthcare system up to $124.5 billion between 2021 and 2025, if they were allowed to come to

market.[12] The manipulative use of patents contributes substantially to total healthcare costs.

Patents *Pro Bono Publico*

Patents were created with two important goals. The first was to stimulate interest in research and find solutions to problems. The second was to protect the interests of the people. The duration of time designated for exclusive use of a new technology or approach was intended to be limited. The innovation would then enter the public domain, for the benefit of all. The granting of a patent was designed to advance the interests of both the inventor and the public.

How can patent laws be improved to ensure both of these goals are met? Priti Krishtel, JD, is the founder and an executive director of the Initiative for Medicines, Access & Knowledge (I-MAK), a nonprofit organization that addresses structural inequities in how medicines are developed and distributed. She suggests the following reforms:[13]

1. *Raise the bar for awarding patents*. We hand out patents worth billions of dollars for trivial changes in drugs. That's like awarding a second Pulitzer prize for the second edition of a previously published book. Patents should be awarded only for truly innovative products that serve an important public need;
2. *Amend incentives for the U.S. Patent and Trademark Office*. The Patent Office's budget depends on fees it collects for patent review, which provides an incentive to move quickly. Providing the Patent Office with an alternate revenue stream would help ensure it provides each patent application with the careful consideration it deserves;
3. *Create a role for public participation*: Public advocates should be allowed to participate in discussions regarding which drugs are worthy of being granted a patent;
4. *Expand legal standing to initiate lawsuits*. Once a patent has been awarded, only another manufacturer with a financial interest in that patent has standing to challenge the patent in court. Patient advocates should be empowered to challenge inappropriate patents; and
5. *Create a public advocate* to monitor the activities of the Patent Office and report to Congress to ensure its activities continue to serve the public interest.

Robin Feldman, professor of law and director of the Center for Innovation at UC Hastings College of the Law, San Francisco, argues for a one-and-done approach to drug patents:[14]

I believe that one period of protection should be enough. We should make the legal changes necessary to prevent companies from building patent walls and piling up mountains of rights. This could be accomplished by a 'one-and-done' approach for patent protection. Under it, a drug would receive just one period of exclusivity, and no more. The choice of which 'one' could be left entirely in the hands of the pharmaceutical company, with the election made when the FDA approves the drug. … The result, however, is that a pharmaceutical company chooses whether its period of exclusivity would be a patent, an orphan drug designation, a period of data exclusivity (in which no generic is allowed to use the original drug's safety and effectiveness data), or something else—but not all of the above and more.

At the heart of these suggestions is the desire to return patent law to its roots and to ensure that it functions *pro bono*.

When you hear the expression *pro bono*, you probably think of someone working for free. The expression is actually an abbreviation of a longer Latin phrase, *pro bono publico*—for the public good. No one is asking drug companies to work for free. Profits are an important motivation to continue investments in new therapeutics and pharmaceutical research. That said, it is time to modernize patent law to ensure that patents continue to work *pro bono publico*. R

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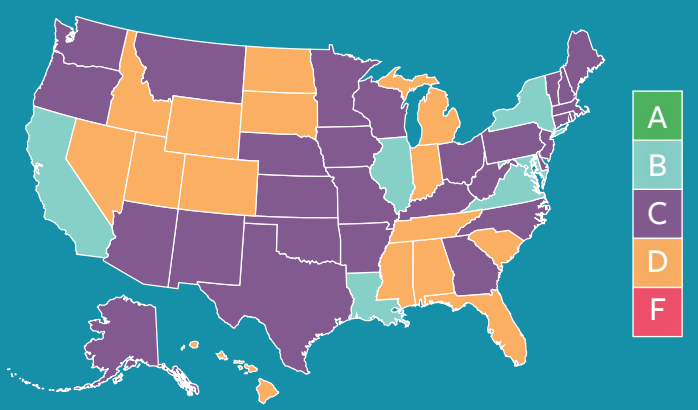
THE RHEUMATIC DISEASE REPORT CARD IS BACK!

September is Rheumatic Disease Awareness Month (RDAM). In recognition of RDAM, the American College of Rheumatology's (ACR) Rheumatic Disease Report Card returns this year, grading each U.S. state and the District of Columbia on how easy it is to live well with a rheumatic disease.



States received letter grades according to their progress on impacting:

ACCESS—How easy it is to see a rheumatologist and receive treatment without insurer-imposed barriers

AFFORDABILITY—What policies are in place to protect patients from high prescription drug costs

ACTIVITY/LIFESTYLE—Measures lifestyle factors affecting the prevalence and severity of rheumatic disease

To learn more, visit acr.tw/reportcard2022

Weathering Storms

We read the article, "Rheumatologists Share Lessons Learned in the Wake of Hurricane Ida" (July 2022; **https://tinyurl.com/3tm69us9**), with great interest. This poignant account of the impacted patients and rheumatologists provides invaluable planning tips regarding medication loss, access to pharmacies and medical records, and strategies to avoid practice losses. The critical lessons presented in this article should be expanded to include other extreme weather events, such as heat waves and air pollutants from massive wildfires, that are expected to occur with greater frequency and ferocity due to climate change.[1,2] Their potential for adverse health outcomes for patients with rheumatic diseases has not been well studied, but as illustrated in this article, major storms can cause a great disruption in the routine delivery of healthcare.[3]

To meet the health needs of our patients and the practice concerns of our providers, the ACR should actively address planning for extreme weather events related to climate change.[4] A starting point would be to post the author's practical planning tips for dealing with major storms on the ACR website for providers and patients. Additional advice regarding the consequences of climate change, such as heat waves and massive wildfires, should be developed and included.

Climate change represents a public health emergency that will continue to pose significant threats to health on multiple levels, even beyond extreme weather events. We are witnessing impacts on air pollution, drought, changes in vector ecology, supply chain issues and food insecurity. This is a watershed moment for our global community and represents an unprecedented opportunity for our medical societies, including the ACR, to step up to help address this challenge. Patient education, advocacy and research have never been so critical.[3]

Sincerely,
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Refractory Cutaneous Lupus

As a dermatologist/internist with a career-long subspecialty interest in the cutaneous manifestations of the rheumatic diseases, I found the case of refractory acute cutaneous lupus by Samantha C. Shapiro, MD, in the June 2022 issue of *The Rheumatologist* (**https://tinyurl.com/jhbafzu4**) intriguing in several ways, and I felt my perspectives on this case might provide additional educational value to the rheumatologist readership.

Diagnosis & Classification

The clinical photos of the patient being discussed suggest a generalized inflammatory skin disorder (i.e., skin lesions both above and below the neck) occurring in the context of a five-year history of systemic lupus erythematosus (SLE). However, the historical duration of the skin changes was not given. The patient's serologic phenotype was very active at the time of presentation, including anti-double-stranded DNA, RNP, Sm and Ro/SS-A autoantibodies, as well as chronically low serum complement levels. In addition, the patient had leukopenia and thrombocytopenia. However, it is stated that the patient had no internal SLE target-organ disease manifestations.

Had a lesional skin biopsy been performed in this case, it could be presumed it would have demonstrated an interface dermatitis, as would be expected for any form of lupus-specific skin disease. Biopsies of acute cutaneous lupus erythematosus (ACLE) and subacute cutaneous lupus erythematosus (SCLE) lesions have a lymphoid cell-rich inflammatory infiltrate focused at the dermal-epidermal junction with damage to the epidermal basal cell layer (i.e., an interface dermatitis). In addition to displaying an interface dermatitis, biopsies of discoid SLE lesions can also show deep reticular dermis inflammation and damaged skin appendages, such as hair follicles and sweat glands, and result in atrophic scarring. This deeper dermal inflammation in discoid SLE lesions can produce clinical induration, which is characteristically not seen in either ACLE or SCLE lesions.

In the case discussion, it was suggested the skin findings consisted of a combination of ACLE and SCLE lesions. In the early epidemiologic studies of SCLE, it was recognized that SCLE can overlap with either ACLE or classic discoid lupus erythematosus in approximately 20% of cases.[1]

The case discussion mentioned scarring alopecia on the posterior scalp of this patient. Neither ACLE nor SCLE produce confluent scarring alopecia of the scalp, nor scarring on other parts of the body. In addition, SCLE lesions are characteristically observed on the trunk, with sparing of the central face. These aspects, plus the prominent papulosquamous scale on the skin lesions of this patient, raise the possibility that she could be suffering from a generalized form of classical discoid lupus erythematosus rather than an overlap of ACLE and SCLE. Although uncommon, discoid lupus erythematosus can involve the "butterfly" distribution of facial skin. And generalized classical discoid lupus erythematosus can, at times, be more refractory to treatment than either ACLE or SCLE.

The case discussion also mentioned the patient had cutaneous changes suggestive of Rowell's syndrome (i.e., erythema multiforme-like skin lesions occurring in context of anti-Ro/SS-A and/or anti-La/SS-B autoantibodies). Presumably that was a reference to the annular palmar skin lesions that were shown in one of the photos of this patient. However, on rare occasion, annular discoid lupus erythematosus skin lesions can preferentially localize to the palmar skin.

Another cause for refractory cutaneous lupus erythematosus is unrecognized drug-induced/drug-exacerbated cutaneous lupus erythematosus. SCLE is now known to commonly be triggered by delayed-in-time hypersensitivity reactions to members of a large number of prescription drug classes (e.g., thiazide diuretics, calcium channel blockers, ACE inhibitors, allylamine antifungals such as terbinafine, protein pump inhibitors, oncologic drugs and others). A list of drugs this patient was taking at the time of lupus erythematosus skin disease onset was not provided in the case summary. In addition to prescription drugs, one must consider certain over-the-counter drugs. As an example, physicians who start patients on prednisone often have the patient start taking an over-the-counter protein pump inhibitor, such as omeprazole, to minimize gastrointestinal side effects due to prednisone. Protein pump inhibitors are one of the more common drug classes that can induce SCLE. However, drug-inducted discoid lupus erythematosus is much less common, if existent at all. Some such published cases of drug-induced discoid lupus erythematosus appear to, in fact, be drug-induced SCLE cases.

It is somewhat anomalous that a patient with such active SLE serologies, leukopenia, thrombocytopenia and persistent hypocomplementemia would have no evidence of internal organ SLE activity or damage. In the context of anti-double-stranded DNA autoantibodies and hypocomplementemia, SLE patients have traditionally been thought to be at increased risk for lupus nephritis. One setting in which this SLE patient's clinical constellation might occur would be in the setting of a genetic complement deficiency state.

Homozygous genetic deficiency of C1q, the first component of the classical complement pathway, is one of the strongest monogenetic associations of SLE. And, C1q-deficient SLE patients frequently exhibit photosensitive forms of cutaneous lupus erythematosus. In addition, genetic deficiency of the C2 and C4 complement components has been associated with SCLE and possibly with discoid lupus erythematosus as well. One might postulate that genetic deficiency of an early classical pathway complement component could be a risk factor for treatment-refractory cutaneous lupus erythematosus. Familial discoid lupus erythematosus patients with heterozygous C2 deficiency have been reported to have a clinical phenotype similar to that of the patient described by Dr. Shapiro.[2] However, the limited anecdotal published literature in this area does not fully support nor refute this hypothesis.

Refractoriness

Over the past four decades I have had many cutaneous lupus erythematosus patients

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IMAGE CASE

Refractory, Acute Cutaneous Lupus

What are the options when the options are running out?

BY SAMANTHA C. SHAPIRO, MD

Refractory cutaneous lupus has limited effective treatment options.

referred to me for "hydroxychloroquine resistance." A good proportion of these patients were found to have been truly resistant to antimalarial monotherapy with hydroxychloroquine. Many of those patients responded to combination antimalarial therapy by adding quinacrine to the hydroxychloroquine for an appropriate period of time. Unfortunately, FDA regulatory actions have resulted in compounded quinacrine not being available on the U.S. market starting in 2016. However, quinacrine recently became available from certain compounding pharmacies that have been unwilling to divulge their source(s). These compounding pharmacies are offering quinacrine at a much higher price, making it unavailable to many patients as coverage of compounded medications by U.S. healthcare insurance organizations is spotty at best. As a result, patients are required to pay the full costs of quinacrine out of pocket more often than not.

It has also been suggested that some patients with cutaneous lupus erythematosus respond to chloroquine when they have not responded to hydroxychloroquine.

For unknown reasons, cigarette smoking has been observed not only to be associated with discoid lupus erythematosus, but can also blunt the clinical effectiveness of hydroxychloroquine therapy in cutaneous lupus erythematosus. This was mentioned in the discussion of the case in question. However, it was not specifically stated whether this patient previously or currently smoked cigarettes.

Another clinical setting in which hydroxychloroquine might not produce clinical benefit for cutaneous lupus erythematosus is when patients are noncompliant in taking the drug. It has been reported that noncompliance in taking hydroxychloroquine accounted for a significant percentage of SLE patients having sub-therapeutic blood levels of hydroxychloroquine.[3]

Until recently, assays of hydroxychloroquine blood levels have required assay techniques such as high-performance liquid chromatography with fluorometric detection that are not compatible with modern high-volume commercial labs. However, progress has recently been made with a capillary electrophoresis-based methodology that might be more compatible with the requirements of modern high-volume commercial testing labs.[4]

Dr. Shapiro concluded the discussion of modern targeted therapy for refractory cutaneous lupus erythematosus with the suggestion that lenalidomide might be considered. Lenalidomide is a derivative of thalidomide thought possibly to have less severe side effects than thalidomide. There is a body of published historical evidence demonstrating that thalidomide can have significant clinical benefit for patients with refractory, active, inflammatory cutaneous lupus erythematosus. Modern evidence suggests that lenalidomide can have a similar benefit for refractory cutaneous lupus erythematosus. The time of onset of clinical benefit of these drugs is quite rapid. However, they both appear to induce short-term anti-inflammatory effects in cutaneous lupus erythematosus rather than long-term remission induction. There is some evidence that SCLE patients can go into long-term remission or convert to milder disease after stopping thalidomide/lenalidomide. This has been reported for SCLE than discoid lupus erythematosus.[5]

Another major problem with such drugs as lenalidomide and thalidomide is their exorbitant costs. Both thalidomide and lenalidomide have FDA-approved indications in cancer therapy. As such, their costs are extremely high in the U.S. In 2022, lenalidomide cost was ~$294,000 per year for the average person in the U.S. Because neither thalidomide nor lenalidomide has been FDA approved for either SLE or cutaneous lupus erythematosus, it would be difficult to convince a patient's commercial medical insurer to cover the high costs of these drugs. However, if a lower income patient meets the company's patient assistance program criteria, they could receive the drugs from the company without cost.

Other drugs that might be of benefit to refractory cutaneous lupus erythematosus include monthly high-dose intravenous immunoglobulin infusion (IVIG), belimumab, JAK/STAT intracellular signaling pathway inhibitors (e.g., tofacitinib, ruxolitinib, baricitinib), and interferon receptor inhibitors (e.g., anifrolumab). Tyk intracellular signaling inhibitors, monoclonal antibodies targeting plasmacytoid dendritic cells (e.g., anti-BDCA2, anti-ILT7) and cGAS-STING intracellular signaling inhibitors could be of potential clinical benefit for refractory cutaneous lupus erythematosus in the future.

While often underappreciated, comparative healthcare quality-of-life studies have shown that chronic skin disease is among the most debilitating of all medical illnesses. As space here is limited, the interested reader can find additional literature citations to relevant points of discussion in the text above in several recently published reviews on this subject.[6]

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Author Response

Thank you so much for your interest in this case.

Skin changes had been present for a total of five years, at which time I assumed care of the patient. A dermatologist had seen the patient a few times and concluded the patient had ACLE and SCLE with features of Rowell's syndrome based on physical exam findings. Skin biopsy was deferred given the high likelihood of cutaneous lupus erythematosus and cost to the patient, who was paying out of pocket for her care. I agree that classic discoid lupus erythematosus is another consideration here, and I very much appreciate your educational discussion.

Your point about refractory cutaneous lupus erythematosus due to an unrecognized drug reaction is another worthy teaching pearl. This patient was not routinely taking any prescription or over-the-counter medications before or during her clinical course, aside from those prescribed for management of SLE.

I, too, was continuously surprised by her lack of end-organ manifestations of disease despite years of active SLE serologies and severe cutaneous lupus erythematosus. Urine studies were closely monitored and consistently normal. A genetic complement deficiency state could indeed explain her SLE variant. Thank you for turning our attention to this interesting entity.

"Hydroxychloroquine resistance" is another valid point. The quotations here are deliberate because compliance plays a well-documented role in patients' "unresponsive to treatment," as your letter aptly cited. Hydroxychloroquine blood levels were deferred given the associated cost, but I do believe the patient was compliant with her medications. We communicated frequently via electronic messages, and she was always forthcoming about her need for refills, as well as cutaneous flares. The addition of quinacrine was suggested by dermatology colleagues, but was price prohibitive.

The patient did not previously or currently smoke.

Regarding therapeutic options for refractory disease, I agree with your diverse suggestions. I'm hopeful new therapies and additional data will provide better answers for these patients in the future. Cost, as you mentioned, continues to be an issue for many.

It's worth noting that the patient's care was not only complicated by severe disease, but limited access. She did not have health insurance. Her family's gross income was too high to qualify for local sliding scale programs, but too low to afford commercial or Marketplace coverage. And even if she had qualified for a local program, biologics and synthetic small molecules wouldn't be covered.[1] She was not approved for lenalidomide's patient assistance program (PAP). She is currently in the process of applying for tofacitinib via PAP. Despite my clinic's extensive experience assisting patients with PAP applications, she is yet to receive the medication.[2]

With gratitude,
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Where Do Rules End & Compassion Begin?

On consideration of DNR & termination of pregnancy

■ **BY JOEL M. KREMER, MD, MACR**

In Brief

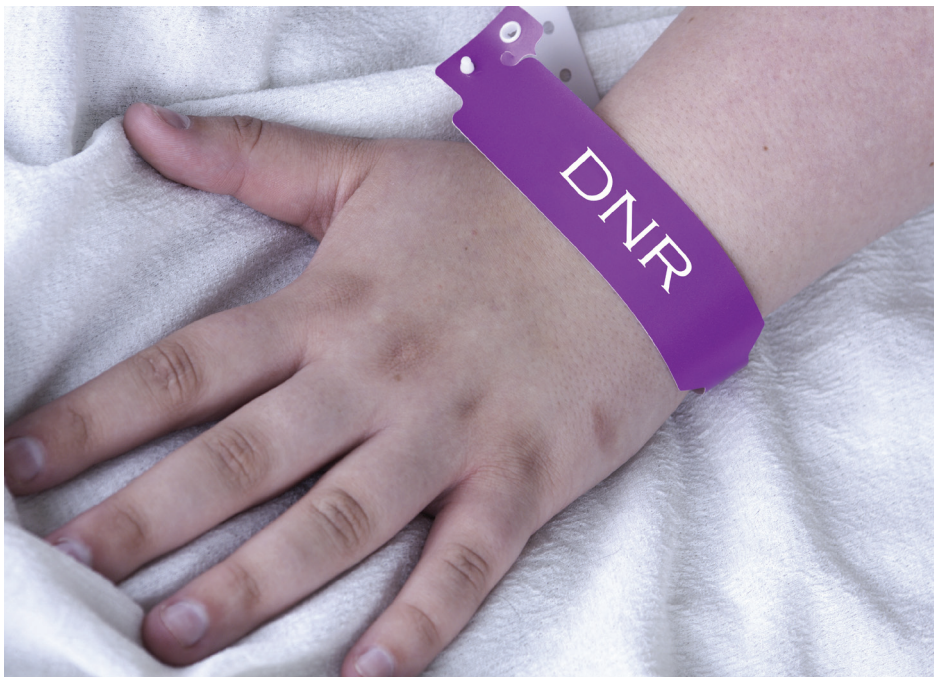
With an example drawn from his case files, Dr. Kremer reflects on the importance of the patient's needs even when they appear to conflict with other directives.

My long-standing patient with CRST syndrome (i.e., calcinosis cutis, Raynaud's phenomenon, sclerodactyly and telangiectasia) had been losing ground over the past 18 months. BL was 54 and had developed restrictive pulmonary disease without radiographic pulmonary infiltrates. Her mean right heart pressures were moderately elevated by ultrasonography.

But the greatest impact on her quality of life and prognosis stemmed from her gut function. BL had swallowing difficulties, along with severely impaired peristalsis throughout the gastrointestinal tract, from the pharynx and esophagus to the large bowel. She had been losing weight, and we had talked about a feeding tube, although that wouldn't help her small bowel hypomotility. Her natural upbeat and exuberant nature had diminished, although she was still capable of genuine smiles during her office visits.

Her loving and supportive husband and daughter would always accompany her to the clinic. I had followed her now for approximately eight years, seeing her five or six times a year. I believed that I knew and understood her and that she and her family knew me. I liked and admired BL. (Yes, we are human, and it follows that we do not develop the same quality of human interactions with each and every human being we see and treat. Is it possible that these positive emotions could affect what we would soon experience together? Should knowing a patient well determine the correctness of any medical approach? More on this later.)

In the past several months, we had had frank discussions about her wishes for end of life. She recognized there were no readily available or easy solutions to the devastating disease that was affecting so many different organ systems. Recovery was highly unlikely, and she knew it. BL told me, in the presence of her family, that she would not want to be on a respirator with a feeding tube. If faced with intubation, she would not wish to have this heroic procedure performed. We agreed that her medical chart would have a do not resuscitate (DNR) order on file with a do not intubate designation.



ANGELA SCHMIDT / SHUTTERSTOCK.COM

Crisis

Within a year of this conversation, I was called at my office in an adjoining building by a house officer who informed me that BL, who had been hospitalized for further gastrointestinal studies, was experiencing what appeared to be a terminal event.

I immediately raced to her hospital room. I found a patient gasping for air while pointing to her throat. Her distraught husband and daughter were at the bedside. They looked at me imploringly. Was this the end? Was she going to die like this?

I quickly glanced around and saw her bedside lunch tray containing a partially consumed chicken dish. BL had a panicked look. Her eyes were wide, her brow furrowed and her mouth stretched in what looked like a ghastly, stifled scream. She just needed to breathe!

I placed a stethoscope over her airway and heard a great deal of inspiratory turbulence. I got behind the chair where she was seated, pulled her up and performed a Heimlich maneuver. Nothing came out of the airway and nothing changed. I asked the senior medical resident, who had just contacted me, to call anesthesia. She hesitated.

It was easy to read the resident's emotions. This patient was a DNR! We exchanged meaningful looks and held each others' gaze for what seemed like an eternity; probably only seconds. A resolute look indicated she would call anesthesia. Now!

The anesthesiologist arrived quickly. BL was moved to the bed and a laryngoscope was placed in her pharynx. A forceps yielded a large, solid piece of chicken.

BL immediately resumed breathing normally. She experienced a glorious and immediately apparent sense of relief. She and her family were visibly joyful. The gratitude was unmistakable. Her husband and daughter also started to breathe again. There were visible tears of relief all around.

However, the senior medical resident, a woman I had interacted with favorably in other clinical scenarios, had now assumed the mantle of the distraught person in the hospital room. I could see by the look on her face that she had just witnessed a faulty outcome because of a flawed approach executed before her eyes by a medical attending. Why did we just save the life of a patient who had a terminal, incurable disease *who was a DNR*!?

After spending some time with my patient I asked the resident to accompany me to a quiet area on the hospital floor.

A Teaching Moment

We had both witnessed the immediate resolution and relief of an event that would indeed, if allowed to proceed to its natural conclusion, have hastened the final resolution of BL's other very significant health burdens. The resident felt what I did was inappropriate. She was appalled that the natural course of events was not allowed to carry the patient forward to the expected outcome

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DR. KREMER

Is it possible to legally render compassion unacceptable?

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from her acute aspiration. She believed her medical duty was to not interfere. What if she died? Wasn't she DNR?

With some effort, I was able to harness my better angels and treat our interaction as a teaching moment.

I explained that a DNR status is meant to apply to resuscitation in the setting of the natural course of a terminal illness. It was not meant as a directive to withhold compassionate, appropriate medical attention in other situations that might arise in the course of a patient's preterminal life. What if BL had fallen in the bathroom, struck her head and was bleeding? Would we withhold first aid and appropriate medical attention? We went through other scenarios in which a patient with a terminal illness still deserved compassionate attention for relief of symptoms, *even while inhabiting DNR status*.

I was struck by the confusion on the part of a good house officer about how to proceed in the situation described. It became apparent to me that her belief was that DNR meant the right thing to do was to not provide medical attention and succor. And this was to be the case even if the acute problem was reversible, and/or only tangentially related to the underlying condition for which the DNR designation had been agreed to by the patient and her family.

Expanded Learning Opportunity

After BL's experience, we arranged for a house staff conference. I wanted to discuss whether it is appropriate to offer care for acute and reversible events in a patient with a DNR order. There was a good deal of shifting in chairs, accompanied by many troubled expressions on the faces of the medical residents in attendance. Some residents were clearly flummoxed by the idea of helping a DNR patient survive—even if an acute medical challenge was readily reversible. It was just so much easier to equate DNR with "stop doing everything."

The house staff's non-verbal communications appeared to indicate, "Why do you need to make our lives more complex? I thought I knew what to do with these patients!"

Are we respecting the rules by rendering care in these situations?

Patient's Perspective

BL passed away at home several months after this hospital event. Her nutritional status had deteriorated further, and toward the end she refused both feedings and parenteral nutrition. I connected with the family at the time of their loss. They once again thanked me for saving a beloved wife and mother from what would have been an agonizingly frightful and unanticipated final moments of life because of an aspiration at lunch. They again related how grateful BL was that she did not pass from this world in that manner.

They also knew BL had a DNR order, but were mystified and concerned about what they had witnessed in her hospital room at the time of the aspiration. They told me how grateful BL and they were for the end of the acute horror they all experienced that day. But they also related that they just couldn't understand why the medical resident was unable to help prior to the final resolution of the problem.

We fondly recalled together the joyful person we knew before her disease closed in on her.

Beyond One

I have asked myself, when I have relived this experience, if my response would have been as rapid if I had not known and liked the patient and her family. What if this was a person I was seeing for the first time? Would the course of events have rapidly played out in the same manner as for BL? Would I have been able to recognize a reversible situation and respond appropriately even for a patient I did not know? Does knowing a patient well affect the manner in which we interpret medical or legal rules in challenging circumstances?

We all have what can at times be a somewhat tenuous connection with the core values of caring, compassion and empathy. What if I were a DNR? Would I be grateful if someone saved me from an agonizing death from aspiration? How can this be wrong? Particularly at a time of acute stress and confusion about the rules regarding when it is right to have this instinct guide responses in the setting of conflicting rules and legal circumstances, can being confident in compassion for a complete stranger provide the needed personal agency to do the right thing?

It is inevitable that we consider how these lessons might apply to other medical situations. We are not gynecologists who now must deal with decisions regarding termination of pregnancy (thankfully). What should they do when a woman seeks to terminate a pregnancy because of a set of overwhelmingly negative personal or medical circumstances? What if this person was indeed a stranger and we were hearing their story for the very first time? Would it make a difference, as it might have for the medical resident who misinterpreted the meaning of a DNR order? Would a familiar feeling of default compassion trigger, and then inform, an appropriate medical approach?

That is, where should caring end and rules and laws take over? Is it possible to legally render compassion unacceptable? **R**

Joel M. Kremer, MD, MACR, has engaged in clinical research for the past four decades. He currently leads a not-for-profit research organization, the Corrona Research Foundation.

ACR Image Competition 2021

Increasing diversity & representation of skin-of-color disease manifestations, part 7

FEATURED IMAGE FROM NORTH AMERICA
SUBMITTED BY KURT BLAKE, MBBS

Saddle Nose & Cauliflower Ear Deformities in Relapsing Polychondritis

These images depict a 32-year-old man who presented with five weeks of left-sided hearing loss, weight loss and discomfort in the nose, ear, chest wall and knee. He had an erythrocyte sedimentation rate (ESR) of 120 mm/hr, and a C-reactive protein level of 225.4 mg/L. The photographs show his nose and ear deformities. **R**

Born and raised in Jamaica, Kurt Blake, MBBS, finished medical school at the University of the West Indies and worked with an orthopedic team in a rural hospital. Later, he joined the faculty of St. George's University, Grenada, West Indies. He is now pursuing a fellowship in rheumatology at the University of Alabama at Birmingham.

ABOUT THE CONTEST

The Rheumatology Image Library (https://images.rheumatology.org) is a highly accessed teaching resource. However, images showing manifestations of rheumatic disease on skin of color are under-represented, creating a significant educational gap. The 2021 Image Competition, held in conjunction with ACR Convergence 2021, encouraged the global rheumatology community to submit images that will help healthcare providers identify rheumatic disease manifestations in skin of color.

Here, we depict the image featured from North America. The images judged Best Overall and People's Choice, as well as other regional winners appeared in previous issues and can be viewed at https://www.the-rheumatologist.org/tag/image-competition or in the Rheumatology Image Library.

 continued from page 1

Prepare

Whatever platform one will be using for online/remote sessions or courses, instructors must learn how to use that platform, allotting time to take a training class and launch test courses.[2,3] Most course learning management systems (LMS; e.g., Blackboard LMS, Canvas LMS, Moodle) have fairly steep learning curves, particularly if one wants to use a variety of their digital tools.

Depending on available resources and online/remote session or course needs, instructors may want to consider using a digital authoring application or platform (e.g., Eduflow, eXe, Google Classroom) or virtual meeting platform (e.g., Google Meet, Webex by Cisco, Zoom). Again, although generally easier to use than an LMS, time must be allotted to learn the applications and platforms.

Online instruction has been lauded for creating more equitable and standardized learning opportunities, but a critical point to remember is that not all learners have access to the same remote environment.[4-6] When planning online courses, instructors must know if their organizations provide technology support to learners with inadequate equipment, software or network bandwidth. With an understanding of the nature and extent of available technology support, instructors can select or develop learning platforms, digital tools and multimedia content that will be accessible to all of their learners.

Depending on the complexities of the planned online/remote session or course, instructors may want to collaborate with online instructional designers, audiovisual technicians and librarians.[7]

- Online instructional designers can help one understand construction considerations for learner access via desktop and mobile devices, strategies for developing synchronous and asynchronous sessions, and uses of available digital tools;
- Audiovisual technicians can help instructors design and develop engaging multimedia content; and
- Librarians can help instructors identify relevant open-access and in-house collection materials to serve as course textbooks and readings, multimedia content, interactive and collaboration activities, and assessments. Obviously, if using print and DVD materials, instructors need to know the number of available physical copies—one may need to put library materials on reserve or limit their circulation. Not so obvious are considerations for using a library's electronic multimedia materials. These materials have vendor license limitations (e.g., the number of users permissible at one time) that may affect how one can incorporate them into an instructional session or course.

Connect

Learner-centered online/remote instruction emphasizes humanization and connection. Humanization entails designing around presence and interaction rather than content delivery.[8] In an online learning environment, where most work is completed asynchronously, learners need to feel connected to instructors and peers.[3] Even in synchronous remote sessions, learners may feel isolated and disconnected.

When designing, developing and implementing online or remote sessions and courses, one should use digital tools that help create and maintain instructor presence. Instructors should also interpret traditional active learning principles through technological and multimedia components to promote learner engagement, interaction and collaboration.

Interestingly, audio and video recordings that feature instructors and learners themselves have a humanizing effect and help learners feel connected to their peers and instructors.[8,9] If recording capabilities are available, consider having online learners create introductory videos.

As with in-person courses, instructors in online/remote environments need to provide learners with a syllabus detailing reading and multimedia assignments, assessment types and dates, grading rubric and instructor office hours. Equally important, instructors need to provide learners with information on available technology support, clear instructions on how to access content and materials via the course platform or organizational library, and expectations for online discussion room and/or virtual classroom interactions and etiquette.

Instructors should also anticipate increased work hours surrounding their online/remote course presence. Beyond an expanded syllabus, instructors should provide learners with welcoming or introductory emails or videos, and must appreciate the importance of asynchronous feedback on assignments and assessments being immediate.[3,6,8,9]

Include Multimedia

Multimedia content is particularly important for engaging online/remote learners. Effective multimedia materials don't serve as decorations to other instructional content, but enhance the learning process. If insufficient multimedia materials are available, instructors need to create them. In online/remote instructional sessions and courses, poor multimedia design and recording gaffs are magnified and distracting for learners. Again, consider consulting an audiovisual technician for help creating engaging multimedia content.

When creating presentations in PowerPoint, Keynote or other presentation program, adhere to visual design principles:

- Develop a theme and create an atmosphere in uncluttered layouts;
- Highlight key points only;
- Try to keep one main idea per slide;
- Alternate text with graphics, illustrations, images or photographs;
- Combine upper- and lowercase text, which the eye sees/reads better;
- Use sans serif fonts (e.g., Arial), which better display online;
- Use high-contrast colors;
- Use clear and concise legends and axis titles in figures and tables; and
- Be sure to clear copyright as needed for images and photographs.

When recording audio and video, instructors should test their voices for breathing and pronunciation issues, for example, plosives (i.e., consonants produced by stopping the airflow using the lips, teeth or palate, followed by a sudden release of air, such as *t*, *k* and *p* [voiceless] and *d*, *g* and *b* [voiced]) and fricatives (i.e., consonants made by the friction of breath in a narrow opening, producing a turbulent air flow, such as *f* and *th*). These issues can often be resolved by using a pop filter and/or a better microphone. Unless adept at navigating web-based resources and databases, use a screen capture tool to create images for insertion into a presentation, then record the presentation. Whether recording audio or video, work from a script or notes to avoid awkward pauses.

The Web Accessibility Initiative website provides guidance on making audio and video recordings accessible (**https://www.w3.org/WAI/design-develop/#media-resource-for-audio-and-video**).[10] Basic guidelines include providing alternative text and audio description for visuals, as well as creating captions for audio and video recordings. Most LMS and digital authoring tools have audio and video recording capabilities with captioning features.

Encourage Active Learning

Online/remote instructors can promote active learning through myriad technological and multimedia components. As with in-person sessions and courses, remote instructors should periodically break from presenting content to engage learners in interactive and collaborative activities.

Virtual meeting platforms include polling and assessment features to help engage learners, as well as discussion and breakout room features to facilitate learner discussion and project collaboration.

Instructors can incorporate active learning activities into online presentations or remote course content. Many LMS audiovisual recording components include the ability to insert questions and feedback into recordings, allowing learners to pace and assess themselves. Most LMS and other digital platforms include learner discussion lists and collaborative work spaces.

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Effective multimedia materials should enhance the learning process, not serve as add-on decorations to other instructional content.

RESOURCES—FIND THE TOOLS

Learning Management Systems

- Blackboard LMS: **https://www.anthology.com/products/teaching-and-learning/learning-effectiveness**
- Canvas LMS: **https://www.instructure.com/canvas**
- Moodle: **https://moodle.org**

Digital Authoring Application

- Eduflow: **https://www.eduflow.com/peer-review**
- eXe: **https://exelearning.org**
- Google Classroom: **https://edu.google.com/intl/ALL_us/workspace-for-education/classroom**

Virtual Meeting Platform

- Google Meet: **https://apps.google.com/meet**
- Webex by Cisco: **https://www.webex.com**
- Zoom: **https://zoom.us**

taltz® (ixekizumab) injection 80 mg/mL

FOR PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS

Rapid ACR20 response seen as early as week 2 in some patients[1-3]

CITRATE-FREE

FDA Approved[4]

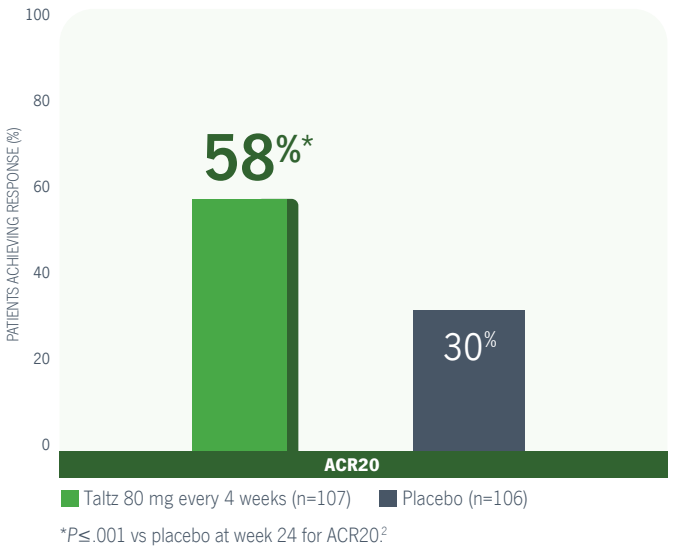
SPIRIT-P1 ACR20 AT WEEK 2: TALTZ 39% VS PLACEBO=13%

SPIRIT-P2 ACR20 AT WEEK 2: TALTZ 38% VS PLACEBO=12%

ACR20 at week 2 was not controlled for type 1 error; therefore, statistical conclusions cannot be made.

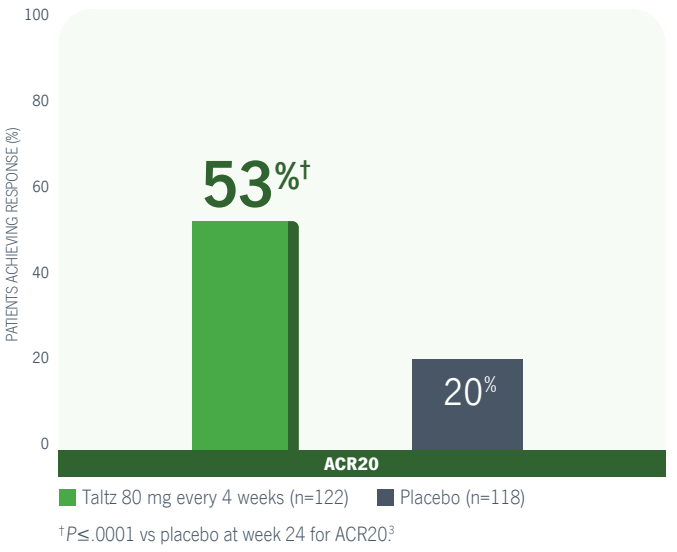
Consistent joint symptom results regardless of TNFi experience[2-4]

SPIRIT-P1 (BIOLOGIC-NAIVE): ACR response rates at week 24, NRI[2,4]



*$P \leq .001$ vs placebo at week 24 for ACR20.[2]

SPIRIT-P2 (TNFi-EXPERIENCED): ACR response rates at week 24, NRI[3,4]



†$P \leq .0001$ vs placebo at week 24 for ACR20.[3]

NRI of intent-to-treat population through week 24.
Inadequate responders (<20% improvement in tender and in swollen joint counts) at week 16 were analyzed as nonresponders after week 16 until the primary endpoint[1]
Primary endpoint=ACR20 response at week 24.

SPIRIT-P1 and -P2 Trial Design[3-6]

SPIRIT-P1 (N=417) and -P2 (N=363) were phase 3, randomized, double-blind, placebo-controlled trials to evaluate the efficacy and safety of Taltz compared with placebo in patients with active psoriatic arthritis. Patients in SPIRIT-P1 were biologic-naive. Patients in SPIRIT-P2 were tumor necrosis factor inhibitor (TNFi)- experienced, having had an inadequate response and/or intolerance to 1 or 2 prior TNFis. In both trials, the primary efficacy endpoint was the proportion of patients achieving ACR20 response at week 24. All patients were ≥18 years of age and had ≥3 swollen and ≥3 tender joints. Patients were randomized to placebo or Taltz 80 mg every 2 or 4 weeks following a 160 mg starting dose. In SPIRIT-P1, an active reference arm of adalimumab 40 mg every 2 weeks was included. Patients in all study arms were allowed to continue taking stable background medications during the trial. Inadequate responders (as defined by blinded criteria of <20% improvement in tender and in swollen joint counts) at week 16 received rescue therapy and were analyzed as nonresponders after week 16 until the primary endpoint. After receiving rescue therapy, inadequate responders in the placebo and adalimumab arms were re-randomized to Taltz 80 mg every 2 or 4 weeks. NRI methods were used for categorical efficacy analyses during the double-blind treatment period.

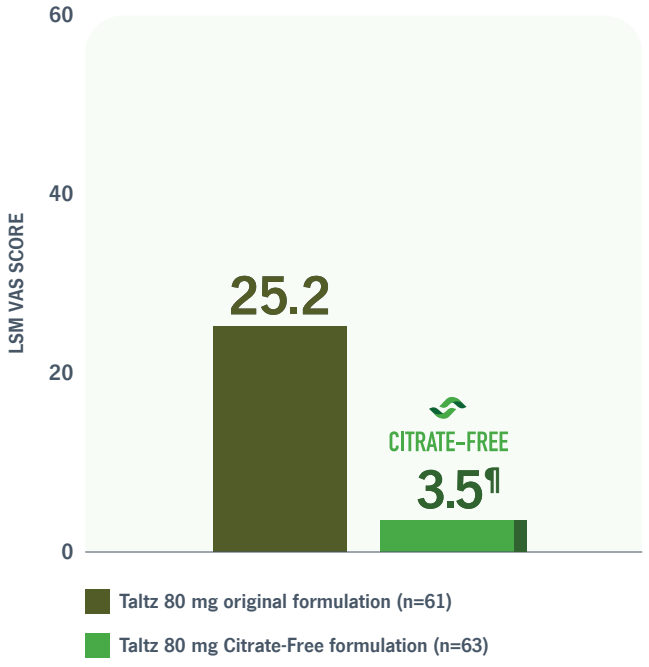
ACR=American College of Radiology; TNFi=tumor necrosis factor inhibitor; NRI=nonresponder imputation.

Please see Important Safety Information on adjacent page.
Please see Brief Summary of Prescribing Information on the following pages. Please see Instructions for Use included with the device.

Taltz is FDA approved in a citrate-free formulation[4]

Same Taltz,‡ less injection site pain§

VAS Injection Site Pain Score Immediately Following Injection[7]



¶*P*<.0001; based on VAS 0-100

‡Same active ingredient

§Vs original formulation; immediately after injection; based on VAS 0-100

Simple transition to Taltz Citrate-Free[4]

- **No new National Drug Codes (NDCs)**
- **No new Rx needed for existing Taltz patients**
- **No new PAs to transition existing Taltz patients**
- **No gaps in therapy**

Once inventory of Taltz original formulation is depleted,
Only citrate-free formulation will be available

VAS=Visual Analogue Scale; LSM=least squares mean; PA=prior authorization.

Taltz Citrate-Free Bioequivalence Study Design[7]
The Citrate-Free Bioequivalence Study (N=245) was a 2-arm, subject-blind, parallel-design study in healthy subjects age 18-75 years to evaluate bioequivalence of Taltz citrate-free (CF) formulation compared to the original formulation of Taltz. Subjects were stratified into 1 of 3 weight categories (low: <70.0 kg; medium: 70.0-80.0 kg; high: >80.0 kg). Participants were then randomized within the 3 weight categories 1:1 to a single subcutaneous dose of either 80 mg Taltz original formulation (n=126) or 80 mg Taltz CF formulation (n=119). Subjects in each group were sub-randomized 1:1:1 to injection site (arm, thigh, or abdomen). Injections were administered by a medical professional using an autoinjector. The primary endpoint was bioequivalence as measured by maximum concentration (Cmax) of serum ixekizumab and area under the concentration versus time curve (AUC) of ixekizumab from time of injection through day 85 and time of injection through infinity.

Taltz Citrate-Free Injection Pain Study Design[7]
Citrate-Free Injection Pain Study (N=70) was a subject-blind, randomized, crossover study in healthy subjects age 18-75 years to determine injection site pain differences between Taltz citrate-free formulation compared to the original formulation of Taltz. The primary endpoint was pain intensity on injection, as measured by VAS Pain 0-100. Subjects were randomized 1:1:1 to receive a single 1 mL subcutaneous injection of 80 mg Taltz original formulation, 80 mg Taltz citrate-free formulation 1 (CF1), or 80 mg Taltz citrate-free formulation 2 (CF2) in 1 of 3 possible treatment sequences on Days 1, 8, and 15 in a 3-period cross-over design. Injections were administered in the abdomen by a medical professional using a prefilled syringe. CF2 is not an approved formulation. Only data on the commercially available CF1 will be presented.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

Taltz is **indicated** for adult patients with active ankylosing spondylitis, for adult patients with active psoriatic arthritis (PsA), and for adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. Taltz is also **indicated** for adult patients and pediatric patients aged 6 years or older with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

Taltz is contraindicated in patients with a previous serious hypersensitivity reaction, such as anaphylaxis, to ixekizumab or to any of the excipients.

WARNINGS AND PRECAUTIONS

Infections
Taltz may increase the risk of infection. In clinical trials of adult patients with plaque psoriasis, the Taltz group had a higher rate of infections than the placebo group (27% vs 23%). A similar increase in risk of infection was seen in placebo-controlled trials of adult patients with psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and pediatric patients with plaque psoriasis. Serious infections have occurred. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue Taltz until the infection resolves.

Pre-Treatment Evaluation for Tuberculosis
Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with Taltz. Do not administer to patients with active TB infection. Initiate treatment of latent TB prior to administering Taltz. Closely monitor patients receiving Taltz for signs and symptoms of active TB during and after treatment.

Hypersensitivity
Serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), occurred in the Taltz group in clinical trials. Anaphylaxis, including cases leading to hospitalization, has been reported in post-marketing use with Taltz. If a serious hypersensitivity reaction occurs, discontinue Taltz immediately and initiate appropriate therapy.

Inflammatory Bowel Disease
Patients treated with Taltz may be at an increased risk of inflammatory bowel disease. In clinical trials, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the Taltz group than the placebo group. During Taltz treatment, monitor patients for onset or exacerbations of inflammatory bowel disease and if IBD occurs, discontinue Taltz and initiate appropriate medical management.

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

ADVERSE REACTIONS

Most common adverse reactions (≥1%) associated with Taltz treatment are injection site reactions, upper respiratory tract infections, nausea, and tinea infections. Overall, the safety profiles observed in adult patients with psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and pediatric patients with plaque psoriasis were consistent with the safety profile in adult patients with plaque psoriasis, with the exception of influenza and conjunctivitis in psoriatic arthritis and conjunctivitis, influenza, and urticaria in pediatric psoriasis.

Please see Brief Summary of Prescribing Information on the following pages. Please see Instructions for Use included with the device.

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References: 1. Data on file. Lilly USA, LLC. DOF-IX-US-0304. **2.** Mease PJ, van der Heijde D, Ritchlin CT, et al; on behalf of SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis.* 2017;76:79-87. **3.** Nash P, Kirkham B, Okada M, et al; on behalf of SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet.* 2017;389:2317-2327. **4.** Taltz. Prescribing information. Lilly, USA. LLC. **5.** Mease PJ, van der Heijde D, Ritchlin CT, et al; on behalf of SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase 3 trial SPIRIT-P1. *Ann Rheum Dis.* 2017;76(suppl):1-30. **6.** Nash P, Kirkham B, Okada M, et al; on behalf of SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet.* 2017;389:2317-2327. Supplementary appendix. **7.** Chabra S, Gill BJ, Gallo G, et al. Ixekizumab citrate-free formulation: results from two clinical trials. *Adv Ther.* 2022;Epub (Incl Suppl Inf):1-11, 1-4. https://doi.org/10.1007/s12325-022-02126-0.

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Taltz® (ixekizumab) injection

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

Plaque Psoriasis—Taltz is indicated for the treatment of patients aged 6 years and older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis—Taltz is indicated for the treatment of adult patients with active psoriatic arthritis.

Ankylosing Spondylitis—Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis.

Non-radiographic Axial Spondyloarthritis—Taltz is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

CONTRAINDICATIONS

Taltz is contraindicated in patients with a previous serious hypersensitivity reaction, such as anaphylaxis, to ixekizumab or to any of the excipients *(Warnings and Precautions)*.

WARNINGS AND PRECAUTIONS

Infections—Taltz may increase the risk of infection. In clinical trials in adult patients with plaque psoriasis, the Taltz group had a higher rate of infections than the placebo group (27% vs 23%). Upper respiratory tract infections, oral candidiasis, conjunctivitis and tinea infections occurred more frequently in the Taltz group than in the placebo group. A similar increase in risk of infection was seen in placebo-controlled trials in patients with pediatric psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis *(Adverse Reactions)*. Instruct patients treated with Taltz to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy, monitor the patient closely and discontinue Taltz until the infection resolves.

Pre-treatment Evaluation for Tuberculosis—Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with Taltz. Do not administer to patients with active TB infection. Initiate treatment of latent TB prior to administering Taltz. Consider anti-TB therapy prior to initiating Taltz in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving Taltz should be monitored closely for signs and symptoms of active TB during and after treatment.

Hypersensitivity—Serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), occurred in the Taltz group in clinical trials. Anaphylaxis, including cases leading to hospitalization, has been reported in post-marketing use with Taltz *(Adverse Reactions)*. If a serious hypersensitivity reaction occurs, discontinue Taltz immediately and initiate appropriate therapy.

Inflammatory Bowel Disease—Patients treated with Taltz may be at an increased risk of inflammatory bowel disease. In clinical trials, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the Taltz group than in the control group *(Adverse Reactions)*. During Taltz treatment, monitor for onset or exacerbation of inflammatory bowel disease and if IBD occurs, discontinue Taltz and initiate appropriate medical management.

Immunizations—Prior to initiating therapy with Taltz, consider completion of all age-appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with Taltz. No data are available on the response to live vaccines.

ADVERSE REACTIONS

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

- Infections *(Warnings and Precautions)*
- Hypersensitivity Reactions *(Contraindications* and *Warnings and Precautions)*
- Inflammatory Bowel Disease *(Warnings and Precautions)*

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

Adult Plaque Psoriasis

Weeks 0 to 12: Three placebo-controlled trials in subjects with plaque psoriasis were integrated to evaluate the safety of Taltz compared to placebo for up to 12 weeks. A total of 1167 subjects (mean age 45 years; 66% men; 94% White) with plaque psoriasis received Taltz (160 mg at Week 0, 80 mg every 2 weeks [Q2W] for 12 weeks) subcutaneously. In two of the trials, the safety of Taltz (use up to 12 weeks) was also compared with an active comparator, U.S. approved etanercept.

In the 12-week, placebo-controlled period, adverse events occurred in 58% of the Taltz Q2W group (2.5 per subject-year of follow-up) compared with 47% of the placebo group (2.1 per subject-year of follow-up). Serious adverse events occurred in 2% of the Taltz group (0.07 per subject-year of follow-up), and in 2% of the placebo group (0.07 per subject-year of follow-up). Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the Taltz group than the placebo group during the 12-week placebo-controlled period of the pooled clinical trials.

Table 1: Adverse Reactions Occurring in ≥1% of the Taltz Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Clinical Trials through Week 12

Adverse Reactions	Taltz 80 mg Q2W (N=1167) (n%)	Etanercept[b] (N=287) (n%)	Placebo (N=791) (n%)
Injection site reactions	196 (17)	32 (11)	26 (3)
Upper respiratory tract infections[a]	163 (14)	23 (8)	101 (13)
Nausea	23 (2)	1 (<1)	5 (1)
Tinea infections	17 (2)	0	1 (<1)

[a] Upper respiratory tract infections cluster includes nasopharyngitis and rhinovirus infection.

[b] U.S. approved etanercept.

Adverse reactions that occurred at rates less than 1% in the Taltz group and more frequently than in the placebo group during the 12-week induction period included rhinitis, oral candidiasis, urticaria, influenza, conjunctivitis, inflammatory bowel disease, and angioedema.

Weeks 13 to 60: A total of 332 subjects received the recommended maintenance regimen of Taltz 80 mg dosed every 4 weeks. During the maintenance period (Weeks 13 to 60), adverse events occurred in 80% of subjects treated with Taltz (1.0 per subject-year of follow-up) compared to 58% of subjects treated with placebo (1.1 per subject-year of follow-up). Serious adverse events were reported in 4% of subjects treated with Taltz (0.05 per subject-year of follow-up) and none in the subjects treated with placebo.

Weeks 0 to 60: Over the entire treatment period (Weeks 0 to 60), adverse events were reported in 67% of subjects treated with Taltz (1.4 per subject-year of follow-up) compared to 48% of subjects treated with placebo (2.0 per subject-year of follow-up). Serious adverse events were reported in 3% of subjects treated with Taltz (0.06 per subject-year of follow-up), and in 2% of subjects treated with placebo (0.06 per subject-year of follow-up).

Specific Adverse Drug Reactions**:**

Injection Site Reactions: The most frequent injection site reactions were erythema and pain. Most injection site reactions were mild-to-moderate in severity and did not lead to discontinuation of Taltz.

Infections: In the 12-week, placebo-controlled period of the clinical trials in plaque psoriasis, infections occurred in 27% of subjects treated with Taltz (1.2 per subject-year of follow-up) compared to 23% of subjects treated with placebo (1.0 per subject-year of follow-up). Serious infections occurred in 0.4% of subjects treated with Taltz (0.02 per subject-year of follow-up) and in 0.4% of subjects treated with placebo (0.02 per subject-year of follow-up) *(Warnings and Precautions)*.

During the maintenance treatment period (Weeks 13 to 60), infections occurred in 57% of subjects treated with Taltz (0.70 per subject-year of follow-up) compared to 32% of subjects treated with placebo (0.61 per subject-year of follow-up). Serious infections occurred in 0.9% of subjects treated with Taltz (0.01 per subject-year of follow-up) and none in the subjects treated with placebo.

Over the entire treatment period (Weeks 0 to 60), infections were reported in 38% of subjects treated with Taltz (0.83 per subject-year of follow-up) compared to 23% of subjects treated with placebo (1.0 per subject-year of follow-up). Serious infections occurred in 0.7% of subjects treated with Taltz (0.02 per subject-year of follow-up), and in 0.4% of subject treated with placebo (0.02 per subject-year of follow-up).

*Inflammatory Bowel Disease: I*n adult subjects with plaque psoriasis, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the TALTZ 80 mg Q2W group (Crohn's disease 0.1%, ulcerative colitis 0.2%) than the placebo group (0%) during the 12-week, placebo-controlled period in clinical trials *(Warnings and Precautions).*

Laboratory Assessment of Cytopenia:

Neutropenia—Over the entire treatment period (Weeks 0 to 60), neutropenia occurred in 11% of subjects treated with Taltz (0.24 per subject-year of follow-up) compared to 3% of subjects treated with placebo (0.14 per subject-year of follow-up). In subjects treated with Taltz, the incidence rate of neutropenia during Weeks 13 to 60 was lower than the incidence rate during Weeks 0 to 12.

In the 12-week, placebo-controlled period, neutropenia ≥ Grade 3 (<1,000 cells/mm^3) occurred in 0.2% of the Taltz group (0.007 per subject-year of follow-up) compared to 0.1% of the placebo group (0.006 per subject-year of follow-up). The majority of cases of neutropenia were either Grade 2 (2% for Taltz 80 mg Q2W versus 0.3% for placebo; ≥1,000 to <1,500 cells/mm^3) or Grade 1 (7% for Taltz 80 mg Q2W versus 3% for placebo; ≥1,500 cells/mm^3 to <2,000 cells/mm^3). Neutropenia in the Taltz group was not associated with an increased rate of infection compared to the placebo group.

Thrombocytopenia—Ninety eight percent of cases of thrombocytopenia were Grade 1 (3% for Taltz 80 mg Q2W versus 1% for placebo; ≥75,000 cells/mm^3 to <150,000 cells/mm^3). Thrombocytopenia in subjects treated with Taltz was not associated with an increased rate of bleeding compared to subjects treated with placebo.

Active Comparator Trials: In the two clinical trials that included an active comparator, the rate of serious adverse events during weeks zero to twelve was 0.7% for U.S.-approved etanercept and 2% for Taltz 80 mg Q2W, and the rate of discontinuation from adverse events was 0.7% for U.S. approved etanercept and 2% for Taltz 80 mg Q2W. The incidence of infections was 18% for U.S. approved etanercept and 26% for Taltz 80 mg Q2W. The rate of serious infections was 0.3% for both Taltz 80 mg Q2W and U.S. approved etanercept.

Pediatric Plaque Psoriasis

Taltz was evaluated in a placebo-controlled trial in pediatric subjects with moderate-to-severe psoriasis 6 to less than 18 years of age. A total of 171 subjects were studied (115 subjects on Taltz and 56 subjects on placebo). Overall, the safety profile observed in pediatric subjects with plaque psoriasis treated with Taltz every 4 weeks is consistent with the safety profile in adult subjects with plaque psoriasis with the exception of the frequencies of conjunctivitis (2.6%), influenza (1.7%), and urticaria (1.7%).

In this clinical trial, Crohn's disease occurred at a greater frequency in the Taltz group (0.9%) than the placebo group (0%) during the 12-week, placebo-controlled period. Crohn's disease occurred in a total of 4 Taltz treated subjects (2.0%) in the clinical trial *(Warnings and Precautions).*

Psoriatic Arthritis

Taltz was studied in two placebo-controlled trials in patients with psoriatic arthritis. A total of 678 patients were studied (454 patients on Taltz and 224 on placebo). A total of 229 patients in these trials received Taltz 160 mg at Week 0, followed by 80 mg every 4 weeks (Q4W). Overall, the safety profile observed in patients with psoriatic arthritis treated with Taltz Q4W is consistent with the safety profile in adult patients with plaque psoriasis with the exception of the frequencies of influenza (1.3%) and conjunctivitis (1.3%).

Taltz® (ixekizumab) injection IX HCP BS 06JAN2022

Ankylosing Spondylitis

Taltz was studied in two placebo-controlled trials in patients with ankylosing spondylitis. A total of 566 patients were studied (376 patients on Taltz and 190 on placebo). A total of 195 patients in these trials received Taltz 80 or 160 mg at Week 0, followed by 80 mg every 4 weeks (Q4W). Overall, the safety profile observed in patients with ankylosing spondylitis treated with Taltz Q4W is consistent with the safety profile in adult patients with plaque psoriasis.

In adult patients with ankylosing spondylitis, Crohn's disease and ulcerative colitis, including exacerbations, occurred in 2 patients (1.0%) and 1 patient (0.5%), respectively, in the Taltz 80 mg Q4W group and 1 patient (0.5%) and 0%, respectively, in the placebo group during the 16-week, placebo-controlled period in clinical trials. Of these patients, serious events occurred in 1 patient in the Taltz 80 mg Q4W group and 1 patient in the placebo group *(Warnings and Precautions).*

Non-radiographic Axial Spondyloarthritis

Taltz was studied in a placebo-controlled trial in patients with non-radiographic axial spondyloarthritis. A total of 303 patients were studied (198 patients on Taltz and 105 on placebo). A total of 96 patients in this trial received Taltz 80 or 160 mg at Week 0, followed by 80 mg every 4 weeks (Q4W). Overall, the safety profile observed in patients with non-radiographic axial spondyloarthritis treated with Taltz 80 mg Q4W up to Week 16 is consistent with the previous experience of Taltz in other indications.

Immunogenicity—As with all therapeutic proteins, there is the potential for immunogenicity with Taltz. The assay to test for neutralizing antibodies has limitations detecting neutralizing antibodies in the presence of ixekizumab; therefore, the incidence of neutralizing antibodies development could be underestimated.

Plaque Psoriasis Population

By Week 12, approximately 9% of adult subjects treated with Taltz every 2 weeks developed antibodies to ixekizumab. Approximately 22% of subjects treated with Taltz at the recommended dosing regimen developed antibodies to ixekizumab during the 60-week treatment period. The clinical effects of antibodies to ixekizumab are dependent on the antibody titer; higher antibody titers were associated with decreasing drug concentration and clinical response.

Of the adult subjects who developed antibodies to ixekizumab during the 60-week treatment period, approximately 10%, which equates to 2% of subjects treated with Taltz at the recommended dosing regimen, had antibodies that were classified as neutralizing. Neutralizing antibodies were associated with reduced drug concentrations and loss of efficacy.

In pediatric psoriasis subjects treated with ixekizumab at the recommended dosing regimen up to 12 weeks, 21 subjects (18%) developed anti-drug antibodies, 5 subjects (4%) had confirmed neutralizing antibodies associated with low drug concentrations. No conclusive evidence could be obtained on the potential association of neutralizing antibodies and clinical response and/or adverse events due to small number of pediatric subjects in the study.

Psoriatic Arthritis Population

For subjects treated with Taltz 80 mg every 4 weeks for up to 52 weeks (PsA1), 11% developed anti-drug antibodies, and 8% had confirmed neutralizing antibodies.

Ankylosing Spondylitis Population

For patients treated with Taltz 80 mg every 4 weeks for up to 16 weeks (AS1, AS2), 5.2% developed anti-drug antibodies, and 1.5% had neutralizing antibodies.

Non-radiographic Axial Spondyloarthritis Population

Of patients treated with Taltz 80 mg every 4 weeks for up to 52 weeks (nr-axSpA1), 8.9% developed anti-drug antibodies, all of which were low titer. No patient had neutralizing antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to Taltz across indications or with the incidences of antibodies to other products may be misleading.

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

Immune system disorders: anaphylaxis *(Contraindications* and *Warnings and Precautions)*

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Taltz during pregnancy. Pregnant women should be encouraged to enroll themselves in the registry by calling 1-800-284-1695.

Risk Summary—There are no available data on Taltz use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, Taltz may be transmitted from the mother to the developing fetus. An embryofetal development study conducted in pregnant monkeys at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus. When dosing was continued until parturition, neonatal deaths were observed at 1.9 times the MRHD *[see Data]*. The clinical significance of these nonclinical findings is unknown.

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

Data

Animal Data—An embryofetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis to near parturition at doses up to 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). These neonatal deaths were attributed to early delivery, trauma, or congenital defect. The clinical significance of these findings is unknown. No ixekizumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

Lactation

Risk Summary—There are no data on the presence of ixekizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Taltz and any potential adverse effects on the breastfed infant from Taltz or from the underlying maternal condition.

Pediatric Use—The safety and effectiveness of Taltz have been established in pediatric subjects aged 6 years to less than 18 years with moderate-to-severe plaque psoriasis. The safety and effectiveness of Taltz in other pediatric indications and for pediatric subjects less than 6 years of age have not been established.

Geriatric Use—Of the 4204 psoriasis subjects exposed to Taltz, a total of 301 were 65 years or older, and 36 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

PATIENT COUNSELING INFORMATION—Advise the patient and/or caregiver to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before the patient starts using Taltz and each time the prescription is renewed, as there may be new information they need to know.

Instructions on Self-Administration: Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the autoinjector or prefilled syringe correctly *(Instructions for Use)*.

Infection: Inform patients that Taltz may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider, and contacting their healthcare provider if they develop any symptoms of infection *(Warnings and Precautions).*

Allergic Reactions: Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *(Warnings and Precautions).*

Pregnancy: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Taltz during pregnancy. Advise patients to contact the registry at 1-800-284-1695 to enroll (*Use in Specific Populations).*

Additional information can be found at www.Taltz.com.

See Instructions for Use accompanying the product device.

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IX HCP BS 06JAN2022

PP-IX-US-5359

Taltz® (ixekizumab) injection IX HCP BS 06JAN2022

CASE REPORT

CPPD Presenting as Pseudosepsis

Practical challenges in the diagnosis remain

BY HASSAN FAKHOURY, BS, ERIN CHEW, MD, & NARENDER ANNAPUREDDY, MBBS

High index of suspicion for CPPD is needed in patients older than 65, even in light of other data that may be mistakenly interpreted as evidence of septic joint.

Calcium pyrophosphate crystal deposition disease (CPPD) is an arthritis caused by the accumulation of calcium pyrophosphate crystals. Despite a prevalence of 4–7% among the adult population in Europe and the U.S.,[1] it has remained a relatively under-recognized disease owing to its many clinical presentations. CPPD may cause an acute mono/oligoarthritis, which may mimic gout or septic arthritis; a chronic arthritis, which may mimic a variety of chronic arthritides (e.g., rheumatoid arthritis, osteoarthritis, ankylosing spondylitis); or a systemic disease, which may mimic sepsis or meningitis. An estimated 25% of initial presentations of CPPD mimic gout or septic arthritis.[1] Severity and timing of pain may truly mimic gout, but acute presentations of CPPD are typically less disabling and take longer for pain to reach peak intensity than gouty attacks.[2]

Although the formal diagnostic criteria have been defined, considerable practical challenges in the diagnosis of CPPD remain. Compared with urate crystals in the context of gout, calcium pyrophosphate crystals are smaller and less birefringent via light microscopy, resulting in less reliability and higher interobserver variability.[3]

We describe the case of a 78-year-old man with a history of gout who presented with acute-onset unilateral knee pain, initially thought to be due to a septic joint, a condition also known as pseudosepsis, an inflammatory arthritis that cannot be differentiated from septic arthritis on the basis of history, clinical presentation or serum lab values.[4]

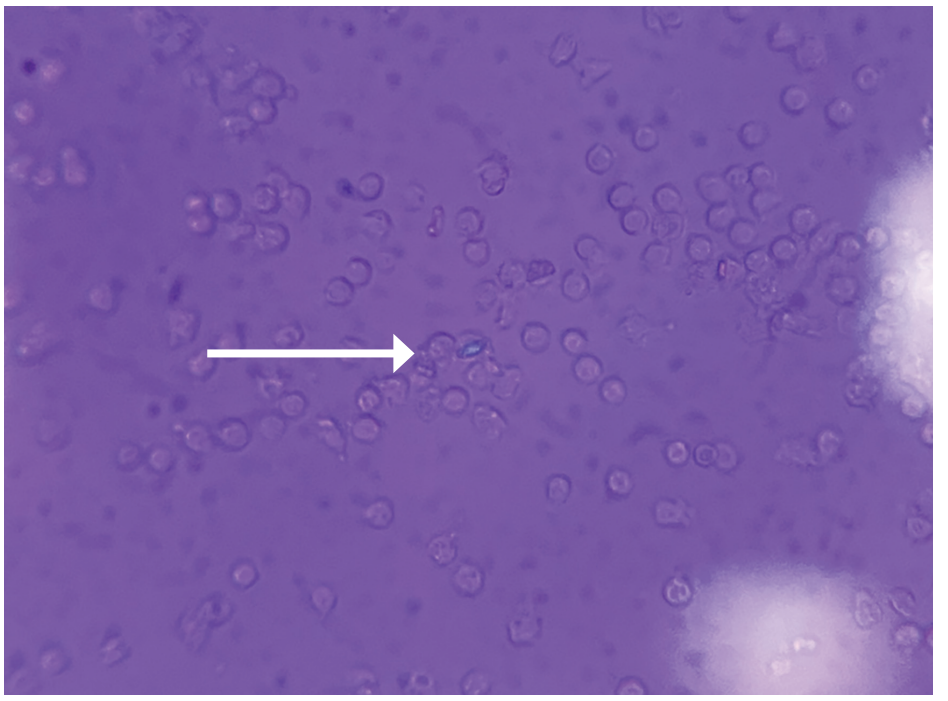
KEY TAKEAWAYS

- Pseudosepsis is an inflammatory arthritis with sterile synovial gram stain and culture that cannot be differentiated from septic arthritis on the basis of history, clinical presentation or serum lab values.
- CPPD has been known to mimic several types of arthritis and systemic conditions due to its varying clinical phenotypes, often resulting in delayed correct diagnosis and inappropriate or over treatment.
- Although a synovial leukocyte count of >100,000 cells/mL is highly suggestive of a septic joint, this does not rule out the diagnosis of a crystalline disease. The presence of persistently sterile cultures should clue the clinician in to an alternate diagnosis.

Case Presentation

A 78-year-old man presented to the hospital with a one-day history of severe right knee pain and swelling. He was completely unable to move the knee or bear weight and was brought in via wheelchair. His pain was exacerbated by movement and light touch. He reported an episode of nausea and vomiting just before his arrival that was presumably due to the pain. The patient denied fevers, chills, night sweats, shortness of breath, chest pain, abdominal pain and diarrhea.

FIGURE 1



Intracellular calcium pyrophosphate crystal on polarized light microscopy.

The patient's medical history was significant for gout, myelodysplastic syndrome and stage 3 chronic kidney disease.

His knee was swollen and palpably warm, but without overlying erythema. His range of motion in the knee was limited due to pain. Initial lab tests revealed a C-reactive protein (CRP) of 295 mg/L (reference range [RR]: 0–5.0 mg/L) and a white blood cell (WBC) count of 14.6k/uL (RR: 3.9–10.7k/uL) with neutrophilic predominance. His right knee X-ray revealed mild tricompartmental joint space narrowing with a large joint effusion but no chondrocalcinosis. Arthrocentesis showed 47,628 nucleated cells (92% segmented neutrophils) and 21,000 red blood cells (RBCs) with no crystals seen via light microscopy. Synovial fluid gram stain was was unrevealing and bacterial cultures yielded no growth. Additional 16s and 18s polymerase chain reaction application studies for the detection of bacterial DNA were negative.

He was immediately taken to the operating room and underwent arthroscopic washout with partial synovectomy. The intraoperative synovial fluid culture failed to yield a culprit organism, although purulent material was noted. After some initial postoperative improvement, his CRP rose to 138 mg/L, prompting an incision and drainage with repeat negative synovial fluid cultures and no bacteria seen in synovial tissue sampling.

He completed a three-week course of antibiotics. However, he remained admitted, with a complex and prolonged hospitalization. Two months later, on hospital day 73, the patient developed acute left knee pain and swelling. Arthrocentesis revealed 42,880 nucleated cells (83% segmented neutrophils), 3,000 RBCs, negative fluid cultures and, once again, no crystals seen via light microscopy. Antibiotics were not initiated at this time given the concern for marrow suppressive effects and the inability to isolate an organism on synovial tissue or fluid culture. He had slow resolution of left knee pain and swelling with conservative pain management.

Three weeks later he had acute worsening of his left knee pain, for which a rheumatologist was consulted. An X-ray of the left knee showed chondrocalcinosis. The serum uric acid level was 8.1 mg/dL (RR: 3.5–7.2 mg/dL). Arthrocentesis revealed 150,927 nucleated cells (90% segmented

neutrophils) and 17,000 RBCs. Synovial fluid gram stain and bacterial culture were again negative.

On our manual review of the synovial fluid, positively birefringent crystals were seen with a polarizing microscope within neutrophils, meeting formal criteria for the diagnosis of acute monoarticular CPPD arthropathy (see Figure 1, opposite). An intra-articular steroid injection was performed. Arthrocentesis was repeated two days after the steroid injection, which revealed 80,600 nucleated cells (64% segmented neutrophils) and repeat visualization of CPPD crystals. He completed a three-day course of anakinra and was discharged home on hospital day 94.

Discussion

The differential diagnosis of acute-onset monoarticular joint pain is relatively limited. It may remain a diagnostic challenge, however, in cases where history, physical and serum lab values fail to adequately support or refute a noninfectious vs. an infectious cause—cases aptly termed *pseudosepsis*.

In addition to CPPD, rheumatoid arthritis, gout, Behçet's disease, systemic lupus erythematosus, ankylosing spondylitis and psoriatic arthritis have all been reported to present as pseudoseptic arthritis.[5] Despite potential fever and leukocytosis, synovial fluid gram stain and culture are repeatedly negative. In one retrospective study across more than two and a half decades at one center, 19% of suspected septic arthritis cases were culture negative.[6]

Several studies have examined the role of synovial WBC count and the percentage of polymorphonuclear cells in the diagnosis of septic arthritis. A leukocyte count of >100,000 cells/mm^3 is highly suggestive of septic joint (likelihood ratio [LR]: 28.0; 95% confidence interval [CI]: 12.0–66.0), and a polymorphonuclear cells percentage of at least 90% further adds to the likelihood (LR: 3.4; 95% CI: 2.8–4.2).[7] The decision to halt antibiotics in light of negative cultures ultimately comes down to clinical judgment, but the presence of persistently negative cultures should clue the clinician in to an alternate diagnosis.[6]

In our case, antibiotics were continued after our patient's initial presentation despite repeated negative cultures and synovial tissue sampling with no bacteria noted. Because no crystals were seen on microscopy and diagnostic uncertainty remained, the decision was made to treat for septic arthritis given its significant morbidity and mortality. What may have given an infectious etiology more credence was the purulent material noted during the first joint washout and the patient's immunosuppressed state. However, it's important to note the possibility of nonbacterial causes for such a finding, as previously described in leukemia and parvovirus-associated pseudosepsis.[6]

A patient's promising response to washout and antibiotics is also unreliable as confirmation for an infected joint as occurred in this case. Improvement following antibiotics may be due to their general anti-inflammatory effect rather than their antimicrobial effects.[6]

The patient's new symptoms on the contralateral side approximately 2.5 months into his hospitalization were compellingly similar to his initial presentation, leading us to believe that CPPD arthropathy was responsible for both instances of his biphasic course. Notably, many observers may have initially overlooked the presence of calcium pyrophosphate crystals, requiring further analysis. The EULAR (the European Alliance of Associations for Rheumatology) highlights that proper training is crucial for the identification of crystals—even one or a few crystals are clinically significant.[8] The absence of chondrocalcinosis on the patient's right knee is also unreliable as this radiologic finding lacks sensitivity and specificity.[8]

Conclusion

This case adds to the many atypical presentations described across the CPPD continuum and highlights the importance of early entertainment of its possibility to avoid unnecessary harm. Our patient remained in the hospital for presumed septic arthritis, which increased his risk for hospital-associated complications that resulted in increased morbidity.

It is important to underscore the clinician's responsibility to always rule out infection while pursuing other possible etiologies. High index of suspicion for CPPD is needed in patients older than 65, even in light of other data that may be mistakenly interpreted as evidence of septic joint, including a high synovial WBC count, absence of chondrocalcinosis and improvement on antibiotics, as we observed in our patient. R

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Remote Instruction Enhanced

continued from page 15

When using such features, online instructors should maintain their presence by monitoring discussion to promote a respectful environment and providing timely constructive feedback on collaborative projects.[11]

Depending upon available resources and online/remote session or course needs, instructors may want to consider using free or low-cost products to engage learners. Many products offer interesting audio-visual, interactive and collaborative features:

- Edpuzzle (**https://edpuzzle.com**) and PlayPosit (**https://go.playposit.com**) allow one to add audio and questions to videos;
- Flip (**https://info.flip.com**) allows one to record videos that learners can asynchronously respond to with comments, audio and video;
- Jeopardy Labs (**https://jeopardylabs.com**) allows one to create and customize simple Jeopardy-like games for small groups;
- Loom (**https://www.loom.com**) is a video messaging tool that allows groups of creators to share multiple short videos;
- Nearpod (**https://nearpod.com**) allows one to create presentations with a wide variety of questions and interactive activities;
- Padlet (**https://padlet.com**) is an online whiteboard that allows multiple users to synchronously post text, documents and multimedia content;
- Quizizz (**https://quizizz.com**) allows one to create gamified activities and assessments;
- Socrative (**https://www.socrative.com**) and Wooclap (**https://www.wooclap.com**) are cloud-based learner response systems; and
- VoiceThread (**https://voicethread.com**) allows users to post and comment on documents and multimedia materials.

All of these products work with a variety of browsers, have varying file size limitations and vary pricing for private and educational users. R

Laura E. Ray, MA, MLS, is the outreach and instructional service librarian at the Cleveland-Marshall College of Law.

Author's note: Inclusion of learning management systems, digital tools and software products in this article does not imply endorsement of those products.

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Understanding the Role of Uric Acid in Gout

Scientific perspectives evolve over time

BY RUTH JESSEN HICKMAN, MD

From the first substantial argument in the 19th century that uric acid played a role in gout, it took about 100 years for the medical community to accept its role in triggering acute inflammatory gout attacks. Two papers, both published in 1962, helped demonstrate the link between uric acid and acute gout attacks, quickly opening the way for successful treatment with urate-lowering therapies.[1,2]

Historical Background

Known to the Egyptians and the Greeks, gouty arthritis was one of the first diseases to be recognized as a distinct clinical entity. Dutch pioneer of microscopy Antonie van Leeuwenhoek was the first to describe the appearance of crystals from a gouty tophus in 1679, although the chemical composition was then unknown.[3] In 1797, the English chemist William Hyde Wollaston, MD, demonstrated the presence of uric acid in gouty tophi, providing some of the earliest evidence of a possible pathophysiologic connection between high uric acid levels and gout.[1]

Garrod's Work

In 1854, English physician Alfred Baring Garrod, MD, described the famous thread test that he had developed—a semiquantitative method for measuring the uric acid in blood or urine. Using it, he demonstrated that most of his gouty patients were hyperuricemic.[1] Through research and his extensive clinical experience, Dr. Garrod came to believe that deposited urate crystals triggered the inflammation response in gouty inflammation.

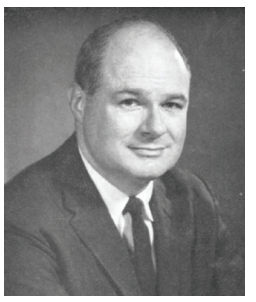

DR. GARROD

Dr. Garrod also carefully distinguished the characteristics of gout from rheumatoid arthritis—then termed *rheumatism*—arguing the two had distinct clinical presentations and underlying disease processes that did not morph into one another. In his mammoth 1876 treatise on the subject, Dr. Garrod noted the following as part of his key characterizations of gout:

> *Uric acid … is invariably present in the blood in abnormal quantities. … True gouty inflammation is always accompanied by a deposition of urate of soda in the inflamed part. … The deposit is crystalline and interstitial. … The deposited urate of soda may be looked upon as the cause, not the effect of the gouty inflammation. … In no disease but true gout is there a deposition of urate of soda in the inflamed tissues.*[4]

However, many did not accept this explanation, and the clinicians of the time continued to debate gout's cause.

In 1899, a young Swiss internist, Max Freudweiler, MD, outlined the debate of the time. He noted that Garrod's followers believed the oversaturation of body fluids led to the deposition of crystalline uric acid salts into the tissues. "This school believes that crystal deposition is the primary step in the development of gouty tophi and therefore attribute tissue necrosis to the damaging effect of the crystals," he said. "In opposition are other authors … who defend the idea that the tissue necrosis of the gouty lesion is the primary event, and the deposition of uric acid salts is secondary to this."[5]


DR. McCARTY

In his own work injecting urate crystals into rabbits, Dr. Freudweiler observed evidence of acute inflammation and tissue necrosis in those injected.[5] Some other early research also found inflammatory reactions resulting from the injection of crystalline uric acids or other forms of urates into living tissue.[5] But much of this work fell into obscurity, and Dr. Garrod's work was left unconfirmed.

Intervening Years

In the following years, the medical community did come to accept a pathophysiologic role between tophaceous gout and hyperuricemia. Salicylates, the first uricosuric agents when given in high doses, and then later agents, such as probenecid, could successfully lower serum urate and gradually dissolve tophaceous gout deposits.[2,3]

Through the 1950s, however, medical texts were noncommittal about the relationship between urates and the pathogenesis of acute inflammatory gouty attacks, and the mechanism of acute gouty arthritis was studied relatively little.[2]

It was well established by then that some, but not all, people with hyperuricemia suffered attacks of acute gouty arthritis. On the other hand, when solutions of non-crystallized sodium urate were injected into humans, this had not seemed to trigger a gout flare, nor did the administration of large doses of uric acid delivered intravenously.[1] At the time, this was a primary point made by those arguing that urates played no role in triggering acute gouty flares.[2]

Modern Study of Gout

One might argue that the modern study of gout began in 1961, with work led by Daniel J. McCarty Jr., MD, then head of rheumatology at the University of Pennsylvania, Philadelphia.[6,7] Using polarized light microscopy, McCarty et al. were able to show crystals of monosodium urate in gouty synovial fluid, often in the process of undergoing phagocytosis. These had been much more difficult to see via the standard light microscopy used previously.

The next year, two key complementary papers in the *Journal of the American Medical Association (JAMA)* and *The Lancet* helped definitively establish the role of elevated serum urate and sodium urate crystals in triggering acute gout flares.[1,2]

The Lancet Article

Dr. McCarty followed up on his important findings in uric acid crystal imaging with his trainee, James S. Faires, MD. Using themselves as the subjects, the two injected uric acid crystals (purified from a gouty tophus and put in solution) into one knee. They injected saline solution without urate crystals into their other knees as a control.[1]

A few hours later, both experienced excruciating inflammatory gout-like sensations in the knees injected with uric acid crystals. Although they had not initially planned on it, the two ultimately opted to take pain medications and hydrocortisone due to the severity of their symptoms. Follow-up experiments in dogs showed a similar effect.[1]

The authors noted, "This preliminary work indicates that sodium urate in crystalline form is probably important in the production of acute gouty arthritis. The exact mechanism response for the intense inflammatory arthritis is unknown … The pathogenesis of the acute gouty attack seems to be related to the deposition of sodium-urate crystals in the synovial fluid."[1]

The authors also pointed out key questions raised by their work, such as: 1) Why are certain individuals with high uric acid blood levels able to keep their urate in solution? 2) Why are certain tissues in the body more susceptible to deposition? 3) What are the factors responsible for the intense response to sodium urate crystals in synovial fluid?[1]

JAMA Article

J. Edwin Seegmiller, MD, and his colleagues at the National Institute of Arthritis and Metabolic Diseases of the Public Health Service (est. 1950; later the National Institute of Arthritis and Musculoskeletal and Skin Diseases), Bethesda, Md., published an important, complementary article in *JAMA* that same year.[2]

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Most previous related work showing an inert inflammatory response to injections had not used crystallized forms of solid sodium urate. In contrast, Dr. Seegmiller and his team injected microcrystalline particulate forms of solid sodium urate into the knees of 12 patient volunteers who had previously had gout disease flares. Each was also injected with an amorphous, non-crystalline solution of sodium urate into the other knee.[2]

Within a couple of hours, all patients showed signs of pain, warmth and/or effusion in the joints injected with the microcrystalline particulate forms of sodium urate. Several patients described their symptoms as similar to those of a spontaneous gouty attack. Aspirated synovial fluid from the joints was examined under polarized microscopy. This revealed leukocytosis and extensive phagocytosis of the urate crystals.[2]

In contrast, injection with the amorphous, non-crystallized solution of sodium urate produced very little inflammatory response, one totally absent in the majority of participants. This was consistent with earlier reports from the 1920s, which had failed to produce an inflammatory reaction using a similar preparation.[2]

"The detailed sequence of events that occurs in the pathogenesis of acute gouty arthritis is yet to be demonstrated experimentally," the authors noted. "We would propose that in order for acute gouty arthritis to develop, the following conditions must be met: 1) Needle-like crystals of sodium urate must be present. 2) An inflammatory reaction against sodium urate crystals must be elicited."[2]

These two papers and other closely related work at the time helped change the paradigm of gout treatment relatively quickly.[1,2] Clinical evidence followed rapidly, which supported allopurinol's use in gout as a urate-lowering therapy.[8] The drug was approved for use in the U.S. in 1966, after which it soon became widely prescribed. And in the ACR's most recent 2020 gout guideline, it is still a cornerstone of preventive gout treatment.[9]

Present Day

In the intervening years, we have learned quite a bit about specifically how urate crystals help initiate and sustain gouty inflammation through stimulating cellular inflammatory responses and how they also can contribute to long-term inflammation and chronic gouty synovitis. We've also learned about some of the local factors hypothesized to play a role in the crystallization of monosodium urate from the blood.[10] But many questions remain.

DR. MIKULS

Ted R. Mikuls, MD, MSPH, the Stokes-Shackleford Professor of Rheumatology and vice chair for research at the University of Nebraska Medical Center, Omaha, was one of the authors of the "2020 American College of Rheumatology Guideline for the Management of Gout."[9]

"Questions that were raised in these articles [from 1962] are still being addressed in our gout guideline, which is kind of amazing," he notes. "To his credit, Garrod was already saying uric acid was a risk factor for gout flares 100 years before these articles were published in the early 1960s. Despite this, the precise links between hyperuricemia and gout flare are still not completely known, but perhaps history tells us not knowing something 60 years later isn't so bad."

Seegmiller et al. noted that, at the time, no consistent relationship had been found between the amounts of uric acid in the blood or urine and acute attacks or remissions; this was one of arguments made by some against a role for serum urate in acute gouty arthritis.

"In 60 years, we haven't fully worked that out," says Dr. Mikuls. "It's not a debate about whether it's the case; it's a debate about the magnitude, about the relationship of a serum urate level on therapeutics."

Whether or not to use a treat-to-target strategy for serum urate and the ideal target level have been debated vigorously in recent years. The American College of Physicians' 2017 guideline did not recommend treating to a specific serum urate target using a serum urate-lowering therapy, such as allopurinol.[11] In contrast, the ACR 2020 gout guideline recommends clinicians treat to a target serum urate of 6 mg/dL to reduce the risk of flares, based on some newer evidence.[9]

"To me," adds Dr. Mikuls, "that is probably the most important concept in the 2020 ACR gout guideline."

Another argument against the idea of uric acid's role in gout flares 60 years ago was the marked hyperuricemia seen in some people without gout. "While we have some more thoughts on that now, the same question was raised in this *JAMA* article from 60 years ago," says Dr. Mikuls. "We still don't really have an answer."

Others at the time argued that elevated uric acid could not be a potential trigger of gouty attacks, as lowering the serum uric acid by uricosuric drugs did not relieve acute attacks of gout. On the contrary, it was known the administration of these drugs might exacerbate an acute attack.

"By the time gout patients have their first flare, they have built up huge urate stores in their body, and it takes a long time to deplete those," Dr. Mikuls explains. "That's one thing we really understand that we probably didn't 60 years ago, that you have to slowly empty that uric acid load, and that takes—with effective conventional therapy—probably a couple of years for most patients."

Similarly, it was known at the time that colchicine, a drug with no effect on uric acid levels, could effectively treat acute gout attacks. This was taken by some as partial evidence that uric acid did not play an important role.

The ACR gout guideline recommends using a prophylactic anti-inflammatory medication, such as colchicine, when first starting patients on urate-lowering medicines, such as allopurinol, to help prevent rebound flares.[9] Dr. Mikuls also points out that many patients—and even some medical professionals—get confused about the different roles in the treatment of gout for anti-inflammatory medications vs. urate-lowering therapies, which can negatively influence medication adherence and flare prevention.

Certainly, self-experimentation by physicians, which played a role in many important and historic medical discoveries, especially in the first part of the twentieth century, is now not viewed through the same lens. "I'd like to find the rheumatologists who would be brave enough to repeat these studies on themselves," says Dr. Mikuls. "Gout is hugely painful. People who get it say, 'This is the worst thing I've ever had.' To do this to yourself is gutsy and shows a high level of commitment and intellectual curiosity." R

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Whether or not to use a treat-to-target strategy for serum urate & the ideal target level have been debated vigorously in recent years.

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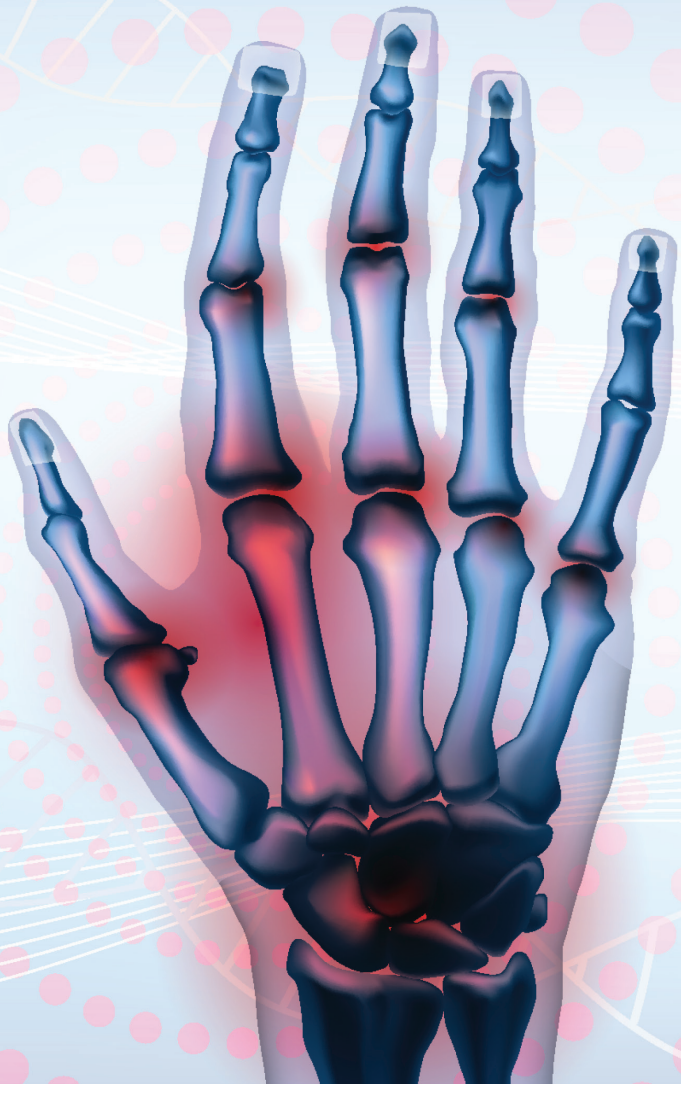
REMISSION DEFINITIONS in RA



Common questions & implications for clinical practice

■ BY SAMANTHA C. SHAPIRO, MD

'Unfortunately, [because] DAS28 yields remission rates far higher than definitions supported by the ACR/EULAR, treatments can appear more effective than they really are if RA trials focusing on remission report only DAS28 remission.'

—Dr. Felson

Defining remission in rheumatoid arthritis (RA) is more important than ever now that we have therapies that put remission within the reach of our patients. David T. Felson, MD, MPH, professor of medicine, Division of Rheumatology, Boston University School of Medicine, and lead author on the 2011 ACR/EULAR RA Remission Criteria and a recent *Arthritis & Rheumatology* editorial that put forth these definitions, offers insight into what remission means for practicing rheumatologists.

2011 ACR/EULAR Definition of Remission in RA

In 2011, the ACR/EULAR published two data-driven consensus definitions of remission in RA that best predicted "absence of X-ray damage progression and good functional outcomes in the future" (see Figure 1, right).[1] The first is a Boolean-based definition that requires a patient to satisfy all of the following: both a tender and a swollen joint count of less than or equal to 1, a C-reactive protein (CRP) level of less than or equal to 1 mg/dL, and a patient global assessment (PGA) of arthritis activity of less than or equal to 1 on a 0–10 scale. The second is a Simplified Disease Activity Index (SDAI) score of less than or equal to 3.3. The SDAI is a sum of the tender and swollen joint counts, CRP level, PGA and provider global assessment of arthritis activity.[2]

The committee recommended that one of these definitions be selected as an outcome and that the results on both be reported in clinical trials. The 28-joint Disease Activity Score (DAS28), a measure still commonly used in clinical trials, was notably absent from recommended remission definitions.

Like all developed criteria, these were "provisionally approved" and await validation in an independent sample for final approval. A final version is expected soon, but an exact date has not been specified.

Since publication of the provisional criteria, three main concerns have arisen: the ongoing use of the DAS28 to define remission in clinical trials, the use of CRP as part of remission definitions and the appropriateness of including PGA in remission definitions. Felson et al. addressed each concern in an editorial in January.[3]

DAS28

Despite a lack of endorsement in the 2011 ACR/EULAR recommendation for use as an RA remission definition, the DAS28 continues to be used in clinical trials. The DAS28 comprises the tender joint count, swollen joint count, PGA

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FIGURE 1: 2011 ACR/EULAR DEFINITIONS OF REMISSION IN RHEUMATOID ARTHRITIS CLINICAL TRIALS

Boolean-based definition:

At any point in time, patient must satisfy all of the following:

- Tender joint count ≤1†
- Swollen joint count ≤1†
- C-reactive protein ≤1 mg/dL
- Patient global assessment ≤1 (on a 0–10 scale)‡

Index-based definition:

At any point in time, patient must have a

- Simplified Disease Activity Index score of ≤3.3§

† For tender and swollen joint counts, use of a 28-joint count may miss actively involved joints, especially in the feet and ankles, and it is preferable to include feet and ankles also when evaluating remission.

‡ For the assessment of remission, we suggest the following format and wording for the global assessment questions. *Format*: A horizontal 10 cm visual analog or Likert scale with the best anchor and lowest score on the left side and the worst anchor and highest score on the right side. *Wording of question and anchors:* For patient global assessment, "Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?" (*Anchors:* very well–very poor). For physician/assessor global assessment, "What is your assessment of the patient's current disease activity?" (*Anchors:* none–extremely active).

§ Defined as the simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and C-reactive protein level (mg/dL).

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and CRP level. However, not all components are equally weighted.

"I co-chaired the ACR/EULAR Definition of Remission Committee in 2011," says Dr. Felson. "We wanted to include the DAS28 because it's so popular, but we couldn't find a threshold—that is, even a very low DAS28 score—that worked because the formula is basically a weighted tender joint count. If your tender joint count is low, you can reach DAS28 remission … even with several swollen joints or an elevated PGA. It doesn't matter what else is going on."

"Practicing rheumatology providers shouldn't be reassured by DAS28 remission in clinical trials," he continues. "Publications often highlight DAS28 remission. Some of these patients have no disease activity … but often that's genuinely not the case. Unfortunately, [because] DAS28 yields remission rates far higher than definitions supported by the ACR/EULAR, treatments can appear more effective than they really are in RA trials focusing on remission report only DAS28 remission."

CRP Levels

The use of CRP levels as part of remission definitions is also imperfect. CRP is the second-most heavily weighted item in the DAS28 formula, but several biologic agents directly reduce CRP regardless of patient status (e.g., interleukin 6 and Janus kinase inhibitors) and several don't reduce CRP even if the patient improves (e.g., rituximab and abatacept).[4]

"Remission definitions that are dependent on acute phase reactants are not serving us well in the new world [in which] some therapies directly target them," says Dr. Felson. "That means we get measures of disease activity that aren't consistent across treatments in clinical trials, which makes it hard to compare efficacy.

"The CRP level is indeed included in the 2011 ACR/EULAR recommended Boolean-based and SDAI definitions for RA remission, but it is not weighted nearly as much as in the DAS28," he clarifies. "Further, there are alternate ACR/EULAR recommended measures of remission that don't include CRP, including the Clinical Disease Activity Index (CDAI) and the three-measure Boolean definition [i.e., tender joint count, swollen joint count and PGA]."

PGA

The appropriateness of including the PGA in remission criteria has also been questioned because the PGA is a subjective measure. We can all agree a patient's assessment of their arthritis activity may be influenced by more than just joint pain and swelling. In addition to fatigue, patients may have a low 28-joint count yet a high PGA score because they have pain in joints the 28-joint count did not include, such as the feet, ankles, hips or neck.

However, Dr. Felson points out that this patient-reported outcome remains a powerful predictor of overall function as measured by the Health Assessment Questionnaire (HAQ), and high PGAs identify those patients whose physical function is worsening.[5] Further, the PGA is a sensitive outcome measure that may shed light on disease activity driven by systemic inflammation.[6]

"We all ask patients, 'How are you doing from an arthritis perspective?' in one way or another," says Dr. Felson. "This is our PGA. If patients say their arthritis is active, they are often right even though a cursory joint exam may miss the source of disease activity. This report of active disease should trigger an evaluation to help determine whether treatment should be changed. On the one hand, they could have pain or fatigue that is unrelated to active RA. Just as likely, though, is that the patient could be fatigued and exhausted due to active RA. Or perhaps there is involvement somewhere beyond what the 28-joint count examined."

When it comes to patients who always report a PGA of 10 out of 10 no matter what, Dr. Felson offers the following advice: "A high PGA should prompt you to look closer. Then, use your clinical judgment to determine if the score is being driven by RA itself or something else, like fibromyalgia."

Editors' Note

Thanks to this editorial, the five journals of the ACR and EULAR jointly agreed to "enforce the use of the products obtained in the course of joint ACR/EULAR or EULAR/ACR activities in all respective papers."[3] For RA, this means the use of ACR/EULAR remission definitions and classification criteria will need to be addressed for manuscripts to be published in these journals. The same will apply for other diseases.

The editors explain that "maintaining uniformity across major publications … not only allows for more appropriate comparison across analyses, but also enhances readers' ability to interpret results."[3]

Conclusion

Defining remission in RA is of utmost importance in a day and age in which remission is within reach. The DAS28 should not be used to define remission because, by this metric, many patients still have swollen joints, and its dependence on CRP values compromises validity with some newer therapies. Although the PGA is subjective, defining remission without including any kind of patient-reported outcome would be remiss. 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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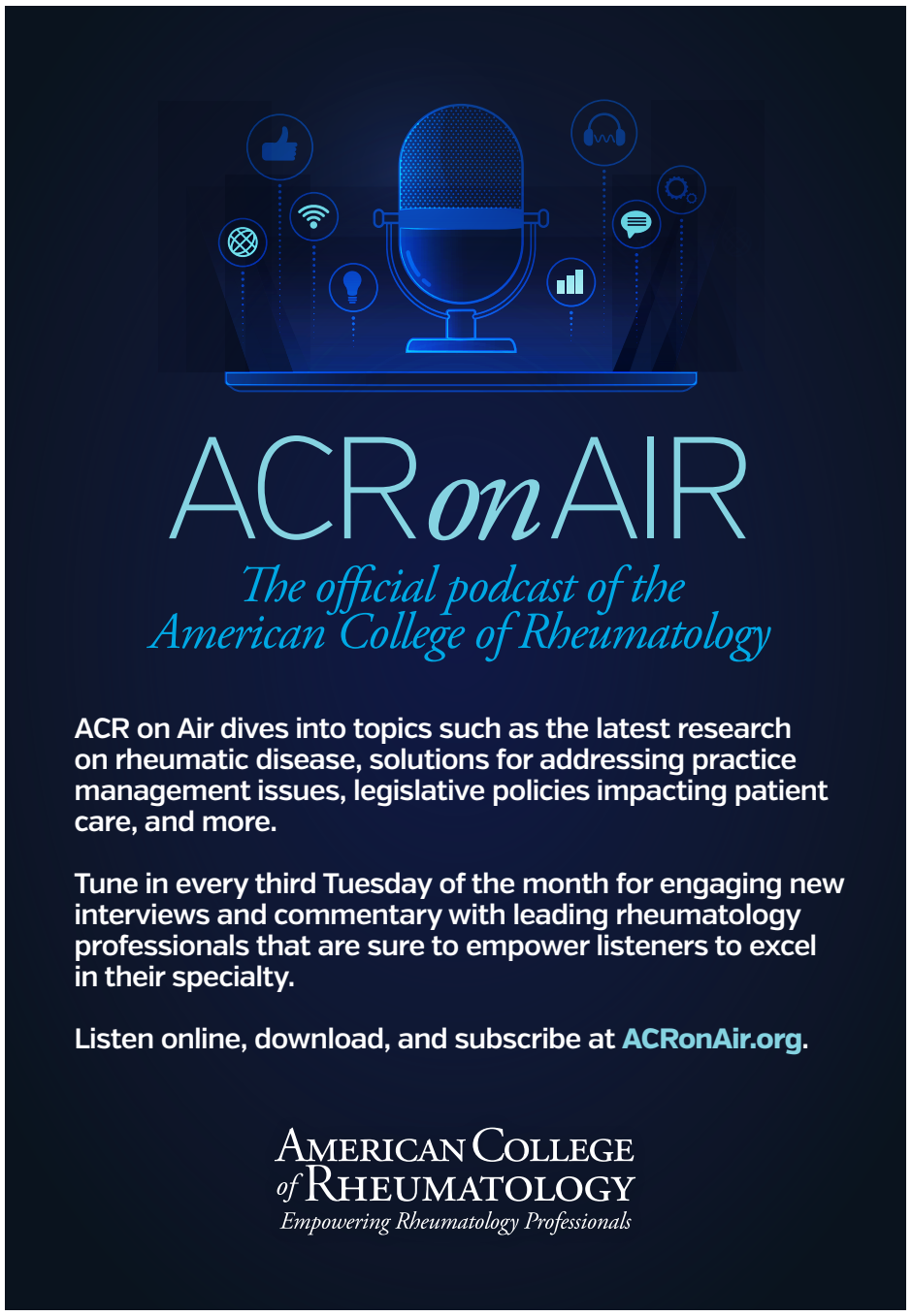
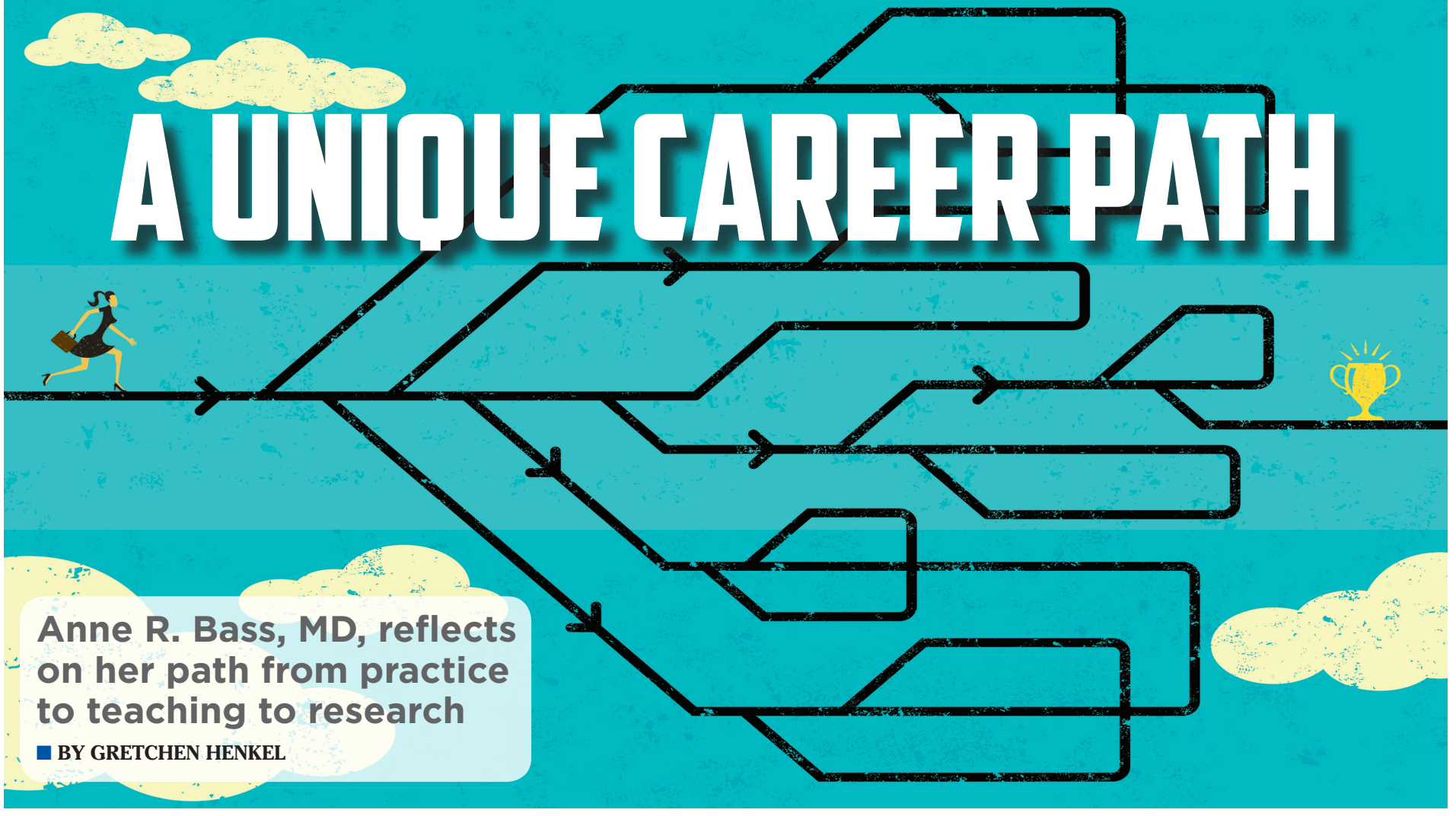


A UNIQUE CAREER PATH



Anne R. Bass, MD, reflects on her path from practice to teaching to research

■ BY GRETCHEN HENKEL

Anne R. Bass, MD, a professor of medicine at Weill Cornell Medical College/Hospital for Special Surgery, New York, has had a unique career path combining clinical practice with academia.

Dr. Bass knew "pretty early" in her academic career that she would be going into medicine. She loved science, but also knew that she wanted to be involved with people. In medical school at Columbia University College of Physicians and Surgeons, New York, she was similarly attracted early on to immunology—just when the function of T cells was beginning to be understood. Excitement about immunology was "in the air," she notes.

And because she also intuited that pure basic science was not her route, she realized rheumatology provided the way to combine research and working with people. "I realized that rheumatology was the clinical side of immunology," she says.

The research and academic threads that now characterize her career were not immediately distinct. Dr. Bass says, "I've had this kind of backward career trajectory," and clinical research is now in the forefront. She shared the situations in which she has capitalized on serendipity and challenge.

The Call of Academics

Dr. Bass conducted research on Lyme disease, which was then endemic in the Northeast, during her fellowship at New York University/Hospital for Joint Diseases. The study entailed obtaining joint fluid specimens from rheumatologists affiliated with Yale University, New Haven, Conn. A site visit to that New Haven practice led to her joining the practice, while her husband began a post in Connecticut as well. This move, she recalls, was "a bit of surprise" and not what she had originally planned to do.

The couple relocated to New York City three years later to support her husband's career, and Dr. Bass joined a Midtown practice affiliated with Columbia. The physical distance from the practice to Columbia made academic involvement difficult, and, she says, "I was feeling cut off [from academics]."

She knew colleagues at the Hospital for Special Surgery (HSS) and in 2000 began showing up for grand rounds and attending conferences there. Stephan A. Paget, MD, FACP, FACR, former physician in chief and chair of the Division of Rheumatology, asked Dr. Bass whether she would like to become affiliated with HSS. Her answer was affirmative, and she spent the next 10 years splitting her time between mornings at her Midtown practice and afternoons at HSS.

In 2005, Dr. Paget offered Dr. Bass a position as associate program director, which led to her joining HSS full time in 2010 as rheumatology fellowship program director.

A 'Roundabout Way' to Clinical Research

As a premier joint replacement institution, HSS also has a large rheumatology division. When Dr. Bass arrived at HSS in the early 2000s, she recalls that quite a bit of controversy revolved around the best way to manage orthopedic patients after surgery to prevent thrombosis. Dr. Paget asked Dr. Bass to head up a task force to formulate guidelines on administration of blood thinners for thrombosis prophylaxis in postoperative patients.

Dr. Bass became involved with the National Quality Forum and then led a small clinical trial at HSS. This work led to her later participating in a large National Institutes of Health-funded anticoagulation trial, a six-year project that yielded two published papers in the *Journal of the American Medical Association*. That on-the-job training in clinical research methodology led to other research projects related to racial disparities and outcomes in orthopedic surgery.

Then, around 2017, clinicians started to see cancer patients treated with checkpoint inhibitors who were experiencing autoimmune side effects of the treatment, including arthritis. Dr. Bass was fascinated by these patients' conditions and got to work helping create a registry in collaboration with rheumatologist Karmela Kim Chan, MD, also at HSS. They collaborated with scientists in the laboratories at HSS and Brigham and Women's Hospital, Boston, and with oncologists at Memorial Sloan Kettering Cancer Center, New York. This line of study, says Dr. Bass, "was the perfect subject at the perfect time."

In 2021, she made the decision to pass the program director baton to others so she could concentrate on seeing patients clinically and doing translational research, thus returning full circle to her love for immunology.

Advice for Fellows

In an article in the December issue of *The Rheumatologist* when the ACR presented her with the Distinguished Fellowship Program Director Award, Dr. Bass remarked, "I've always thought of myself as Merlin in *The Once and Future King*, living life backward, practice to teaching to research." That said, while she was rheumatology fellowship program director, Dr. Bass cautioned her trainees not to model their careers on her career trajectory.

She has urged fellows to be realistic if their career goal is to be a researcher because to qualify for new investigator and other types of grants requires focus. By the same token, a plan to go into clinical practice could also include a component of collaboration with researchers.

Hearing her story of a roundabout arrival at her passion may help younger trainees, she believes. "Fellows often think the first job they take after fellowship is going to be *it*. They have tremendous pressure and may feel that if they make the wrong decision it will affect their whole life. But life is long, and there is plenty of time to do plenty of things!" R

Gretchen Henkel is a health and medical journalist based in California.

DR. BASS

'I've always thought of myself as Merlin in *The Once and Future King*, living life backward, practice to teaching to research.'

—Dr. Bass

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Scleroderma & ILD

Practical tips on the diagnosis & management of systemic sclerosis-associated interstitial lung disease

■ BY SAMANTHA C. SHAPIRO, MD

DR. HUMMERS

> **For clinical SSc-ILD without extrapulmonary manifestations, Khanna et al. recommend mycophenolate mofetil as a first-line treatment given its favorable toxicity profile compared with cyclophosphamide.**

In September 2019, nintedanib became the first treatment approved by the U.S. Food & Drug Administration (FDA) to slow the rate of decline in pulmonary function of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).[1] FDA approval of tocilizumab for the same indication followed in March 2021.[2]

As rheumatology providers, we can all agree that additional treatment options for systemic sclerosis (SSc)—especially those with FDA approval—are a welcome change to the SSc treatment landscape. However, no one-size-fits-all approach exists for the care of patients with SSc and pulmonary involvement. SSc and SSc-ILD are clinically heterogeneous, and optimal pulmonary monitoring and therapeutic strategies are not yet clearly defined.

In January 2022, Khanna et al. published a clinically relevant review on the diagnosis and treatment of SSc-ILD and proposed a clinical approach for risk stratification and therapeutic management in a clinical context. In this article, we discuss their recommendations and offer additional input from another SSc expert, Laura K. Hummers, MD, co-director, Johns Hopkins Scleroderma Center, associate professor of medicine, Division of Rheumatology, Johns Hopkins University, Baltimore.[3]

Background

SSc is a heterogenous autoimmune disease with the highest individual mortality of all rheumatic conditions.[4] Over the past decade, research has focused on defining clinical subtypes of SSc to predict disease course and better tailor therapies. Clinical subtypes are stratified by degree of skin involvement (i.e., limited vs. diffuse) and autoantibody seropositivity.[5]

Given the efficacy of angiotensin-converting enzyme inhibitors in scleroderma renal crisis, SSc-ILD is now among the leading causes of SSc-related death.[6] The prevalence of SSc-ILD depends on multiple factors, such as screening strategy (i.e., high-resolution computed tomography [HRCT] vs. pulmonary function tests [PFTs]); however, national observational registries and international cohorts show that approximately 65% of SSc patients have or will develop SSc-ILD at some point during their disease course.[7,8]

In 2006 and 2016, the results of two scleroderma lung studies changed practice patterns in SSc-ILD after demonstrating the benefits of cyclophosphamide (CYC) and mycophenolate mofetil (MMF). However, neither treatment has been FDA approved for this indication to date.[9,10]

Regarding FDA-approved therapies, the Safety and Efficacy of Nintedanib in SSc (SENSCIS) trial showed the agent, an anti-fibrotic tyrosine kinase inhibitor, slowed the rate of decline in pulmonary function in patients with SSc-ILD.[11] Tocilizumab, an anti-interleukin 6 receptor antagonist, was studied in patients with SSc and early, diffuse cutaneous disease and elevated acute phase reactants. Although the primary end point for improvement in skin fibrosis was not met, forced vital capacity (FVC) data indicated that tocilizumab may preserve lung function in this population.[12] A follow-up trial demonstrated that preservation of percent predicted FVC was greater with tocilizumab treatment than placebo, leading to the FDA approval.[13]

Diagnosis & Screening of SSc-ILD

Khanna et al. reviewed the evidence supporting the use of both HRCT and complete PFT for the initial screening and diagnosis of SSc-ILD.[14] They recommend baseline HRCT and PFT in all patients with SSc. They reasoned that PFTs alone aren't adequate because values may be normal early in the course of disease.[6]

Dr. Hummers offers a slightly different take. "At our center, all SSc patients get baseline and follow-up PFTs to evaluate for evolving SSc-ILD and pulmonary hypertension," she says. "We don't perform HRCT on all patients because there are lower risk subsets for whom this likely isn't necessary. However, this is a nuanced decision, and it may be safer to just say everyone needs one.

"My real concern is that routine HRCT may lead to low-risk patients with mild SSc-ILD receiving unnecessary, expensive and potentially toxic treatment. Let's say you refer a patient with limited cutaneous disease, anti-centromere antibody positivity and mild SSc-ILD to a pulmonologist. This patient is probably at very low risk of ILD progression, but pulmonologists may think about these patients as similar to the patients with idiopathic pulmonary fibrosis they treat most often. Nintedanib could be prescribed … [for a] patient [who should never be exposed to [it]."

Differentiation & Risk Stratification of SSc-ILD

Khanna et al. recommend the differentiation of subclinical from clinical SSc-ILD and risk stratification of patients at low vs. high risk of SSc-ILD progression (see Figure 1, opposite). These terms are defined as:

- *Subclinical SSc-ILD:* an absence of clinical symptoms, minimal SSc-ILD findings on HRCT and a normal or stable FVC;
- *Clinical SSc-ILD:* clinical symptoms with either SSc-ILD on HRCT and/or abnormal or clinically meaningful decline in FVC or diffusing capacity of the lungs for carbon monoxide (DLCO); and
- *High risk of progressive SSc-ILD:* patients with progressive skin disease, anti-topoisomerase I (anti-Scl-70) antibody positivity or elevated acute phase reactants.

Khanna et al. recommend treatment for patients with clinical SSc-ILD or subclinical SSc-ILD with a high risk of disease progression. Those with subclinical SSc-ILD with low risk of progression require close monitoring (at least every six months) to confirm stability. Monitoring should involve assessment for new or worsening symptoms, PFTs (FVC and DLCO), a six-minute walk test and HRCT as indicated.

Initial Treatment of SSc-ILD

If treatment is indicated for a patient, which therapy should we choose? It's truly the dawn of a new era in rheumatology when the question is not "What drug?" but which to use. Khanna et al. recommend basing treatment decisions on the presence of extrapulmonary manifestations of disease. Dr. Hummers agrees with this approach, noting "the treatment approach for clinical SSc-ILD is similar at our institution."

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For clinical SSc-ILD without extrapulmonary manifestations, the authors recommend MMF as a first-line treatment given its favorable toxicity profile compared with CYC. They also list nintedanib as an option.

Dr. Hummers practices similarly, using MMF as a first-line treatment. If patients are unable to tolerate MMF, she'll switch them to nintedanib if there are no extrapulmonary manifestations of disease that warrant use of a different immunomodulatory drug.

"Of note, if patients don't tolerate MMF due to GI [gastrointestinal] side effects, the chances of them tolerating nintedanib are low, in my experience. Patients often run into the same GI side effects with nintedanib," she says.

For clinical SSc-ILD with active extrapulmonary manifestations, the authors recommend MMF or tocilizumab as a first-line treatment. CYC and rituximab are also options. They note that up-front combination therapy with MMF and nintedanib may be considered in patients with rapidly progressive pulmonary disease. Nintedanib monotherapy is not recommended given a lack of proven benefit for skin or musculoskeletal manifestations of disease.

"I select a therapy based on what will treat the most symptoms," says Dr. Hummers. "If they have lung plus skin or lung plus muscle [involvement], I opt for MMF. If they have lung plus joints, I'd consider tocilizumab. However, the problem with tocilizumab is that the population studied was so narrow. These were patients very early in their disease course with diffuse cutaneous disease. They didn't all have ILD, and you had to have elevated acute phase reactants to be included in the trial. So it's tough to know what the true impact of tocilizumab is on lung disease outside of this narrow target population."

For subclinical SSc-ILD at high risk of progressive disease, the authors recommend tocilizumab as a first-line therapy given the evidence from tocilizumab trials.[14] MMF and CYC are also listed as options; however, randomized controlled data do not currently exist to support the use of one treatment over the other in this regard.

This last bit is where Dr. Hummers' approach differs the most from that suggested by Khanna et al. "I would argue that there are still some people in this group [subclinical SSc-ILD at high risk of progressive disease] who I would still just watch," she says. "For example, patients with limited cutaneous disease, anti-centromere antibody positive, elevated acute phase reactants and mild ILD; or patients with limited cutaneous disease, anti-Scl-70 positivity and mild ILD. I wouldn't automatically reach for tocilizumab [for] these patients, especially given the narrow population studied in the trials, their expense and the potential for toxicity."

Treatment of Progressive SSc-ILD

Should a patient's pulmonary disease progress while they are on the initial regimen, the authors recommend:

- Switching therapies;
- Considering combination immunomodulatory therapy (e.g., MMF plus tocilizumab) or adding nintedanib; and
- Considering hematopoietic stem cell transplant or lung transplant.

Dr. Hummers agrees. When it comes to adding nintedanib, she says, "I am almost always using it in someone who has or is at risk for progressive ILD. In the nintedanib trial, a subset analysis showed the lowest amount of lung function decline was in those taking combination MMF and nintedanib. The study wasn't powered to look at the effect of combination therapy, but we can infer that combo therapy may be beneficial."

Future Directions

Regarding the future direction of research in SSc-ILD, Dr. Hummers says, "For me, there are two burning questions: 1) Outside the narrow population studied in the tocilizumab trials, is there any role for tocilizumab in ILD?; and 2) Is there a population of patients who should get combination MMF and nintedanib up front?"

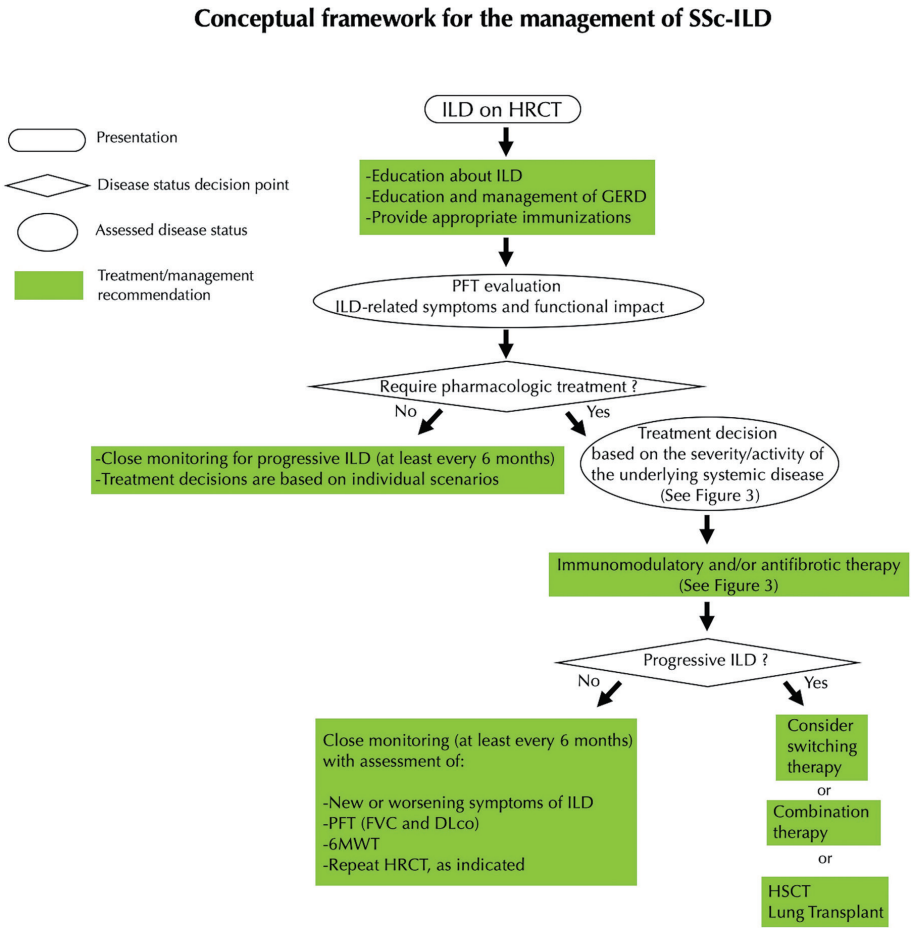
In summary, Khanna et al. provide a practical approach to the care of patients with SSc-ILD that serves as a valuable resource to practicing rheumatology providers.

Dr. Hummers offers additional expert insight on the impact and incorporation of new trial data on clinical practice.

Treatment choices should consider disease severity, risk of progression and extrapulmonary disease activity. Baseline PFTs should be acquired in all patients with SSc, with consideration of HRCT in most patients. In those with subclinical SSc-ILD at high risk of progression, treatment may also be considered. **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 received her training in internal medicine and rheumatology at Johns Hopkins University, Baltimore. She is also a member of the ACR Insurance Subcommittee.

FIGURE 1: EXPERT OPINION ON THE MANAGEMENT OF SSc-ILD



Conceptual framework for the management of systemic sclerosis–associated interstitial lung disease (SSc-ILD). HRCT = high-resolution computed tomography; GERD = gastroesophageal reflux disease; PFT = pulmonary function test; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; 6MWT = 6-minute walk test; HSCT = hematopoietic stem cell transplantation.

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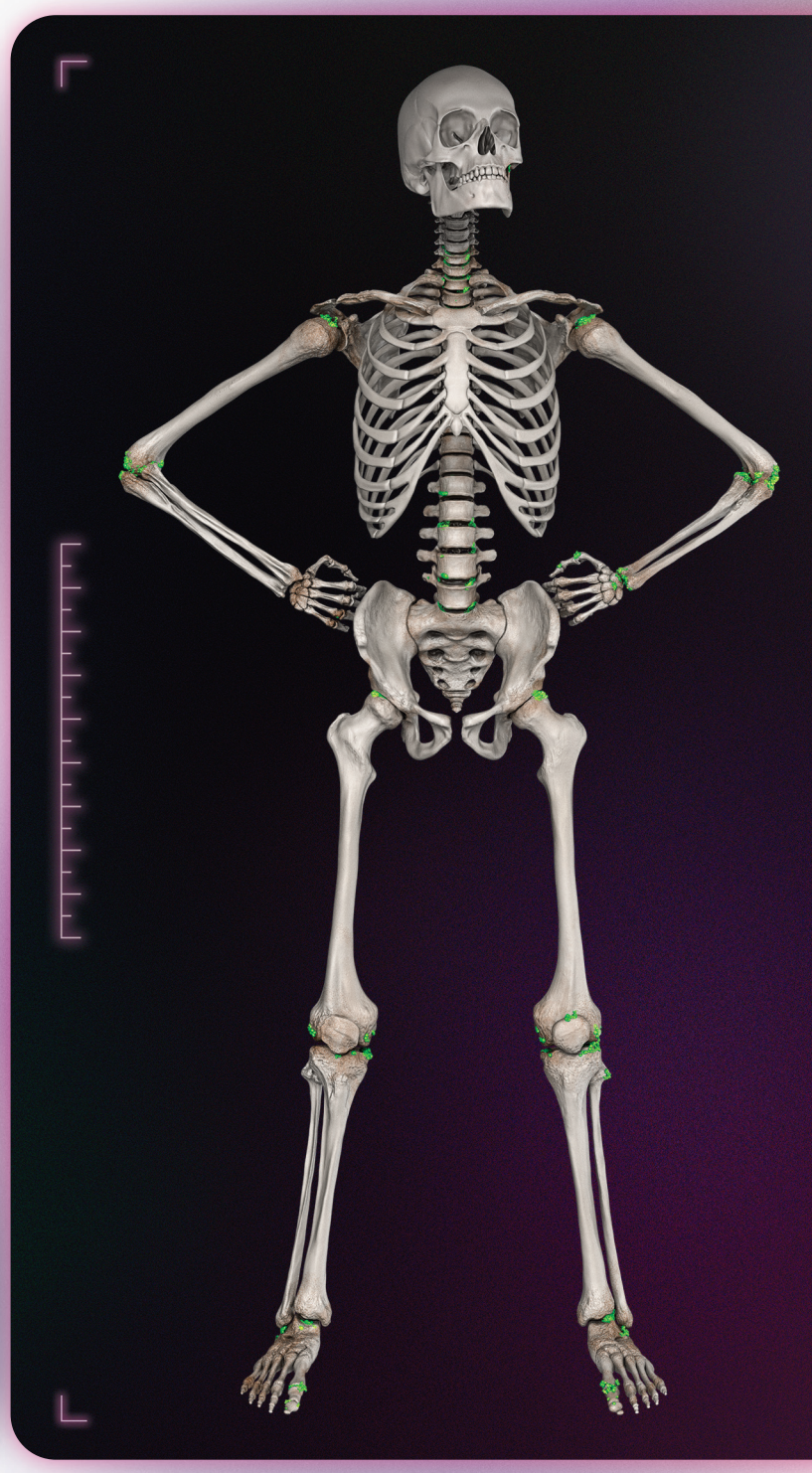
SSc-ILD is now among the leading causes of SSc-related death.



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]

DECT SCAN
AT 6 MONTHS

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.

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KRYSTEXXA®
pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

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

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

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Anaphylaxis

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

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

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

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

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

Infusion Reactions

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

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

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

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

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

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

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

Gout Flares

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

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

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

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

Congestive Heart Failure

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

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

Re-treatment with KRYSTEXXA

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Co-administration with Methotrexate

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

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

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

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

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

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

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

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

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

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

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

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

Immunogenicity

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

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

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

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

Postmarketing Experience

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

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

DRUG INTERACTIONS

Methotrexate

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

PEGylated products

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

Anaphylaxis and Infusion Reactions

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

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

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

Gout Flares

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

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Predicting the Future

Prognostication in rheumatoid arthritis

■ BY JASON LIEBOWITZ, MD

EULAR 2022 (VIRTUAL)—When a patient is diagnosed with rheumatoid arthritis (RA), several questions often come to mind: How does this affect life activities? Will I develop joint deformities? What can I expect my future to look like? At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), an abstract session on the subject of prognosis and prediction in RA highlighted several fascinating research projects that help clinicians better understand how to respond to patients when they ask these questions.

Active Discordance

Rudresh Shukla, MD, clinical research fellow in rheumatology, Division of Musculoskeletal and Dermatological Sciences, University of Manchester, England, delivered the first talk, which was on the subject of discordance between certain disease activity scores and ultrasound findings in patients with RA. Dr. Shukla introduced the concept of active discordance, in which the Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28ESR) score for a patient indicates active disease but synovitis is not found on power Doppler ultrasound, and remission discordance, in which the DAS28ESR score indicates disease remission but synovitis is seen on power Doppler.

Dr. Shukla et al. used data from the VERDERA trial (i.e., very early etanercept and methotrexate vs. methotrexate with delayed etanercept in RA) to analyze features related to active and remission discordance and concordance—the latter meaning that DAS28ESR and ultrasound findings are consistent and both show either disease activity or remission.[1]

In an evaluation of the 120 patients in this study, several trends were noted. First, about one-third of patients transitioned from active concordance at baseline to active discordance early on with treatment. Second, a sizable number of patients continued to show active discordance despite disease-modifying treatment. Third, early treatment with etanercept, together with methotrexate, increased the probability of imaging and clinical remission, even as early as week 12. Finally, the presence of power Doppler tenosynovitis at baseline was a predictor of DAS28 remission with or without synovitis seen on power Doppler ultrasound.

Tenosynovitis on MRI

In the second talk, Nikolet K. den Hollander, MD, PhD, research physician, Leiden University Medical Center, the Netherlands, discussed the value of magnetic resonance imaging (MRI) in detecting rheumatoid arthritis early on in patients with contemporary undifferentiated arthritis. For this study, contemporary undifferentiated arthritis was defined as a patient with features of rheumatoid arthritis who did not meet either the 1987 or 2010 ACR/EULAR classification criteria for RA.[2] Den Hollander et al. looked at undifferentiated arthritis patients in the Leiden early arthritis cohort from 2010 to 2020.

At baseline, these patients underwent MRI of the hands and feet and were evaluated for swollen joint count, positivity for rheumatoid factor and anti-citrullinated protein antibodies (ACPA), and elevation of C-reactive protein. The primary outcome measure was development of RA at one year of follow-up.

The researchers found that tenosynovitis, as seen on MRI in these patients, was independently associated with RA development, especially among patients with the absence of rheumatoid factor and ACPA. In patients without tenosynovitis in oligoarthritis or polyarthritis, essentially no progression to RA was seen.

These data are helpful in both preventing overtreatment and identifying patients at higher risk of progression to RA, although Dr. den Hollander noted that implementation of such routine use of MRI in real-world clinical practice may be challenging.

Synovial Tissue Macrophages

In the third lecture, Stefano Alivernini, MD, PhD, consultant in rheumatology, Catholic University of the Sacred Heart, Milan, Italy, talked about the transcriptomic signature of sustained remission in RA as seen in synovial tissue macrophages. Essentially, Alivernini et al. sought to evaluate the histological composition of synovial tissue in RA patients who were in sustained clinical and ultrasound remission.[3] The researchers hoped to identify synovial biomarkers that are predictive of disease flares or, conversely, of disease remission using histology, macrophage phenotyping and spatial transcriptomics.

The researchers found that synovial tissue enhancement of macrophages positive for MerTK (a member of the Tyro-Axl-MerTK family of receptor tyrosine kinases) was associated with remission maintenance in RA patients in sustained remission after treatment modification.

In addition, digital spatial profiling analysis revealed unique transcriptomic signatures of lining and sublining macrophages in patients in remission that are then associated with subsequent disease flare after treatment modification.

By understanding RA on this molecular level, researchers and clinicians may one day be able to identify features that predict maintenance of remission or high likelihood of relapse of disease.

2 New Antibodies

Later in the session, Diane van der Woude, MD, PhD, rheumatologist and head of the Outpatient Clinic, Leiden University Medical Center, the Netherlands, spoke about two new antibodies that may be relevant in patients with seronegative RA. Dr. van der Woude noted that anti-malondialdehyde-acetaldehyde (anti-MAA) antibodies have, in the past, been described in patients with seropositive and seronegative RA, osteoarthritis, systemic lupus erythematosus and a number of cardiovascular diseases.

Anti-advanced glycated end-products (anti-AGE) antibodies have been seen in patients with diabetes and cardiovascular disease, but some data indicates that, in RA, these antibodies may correlate with disease activity.

In evaluating nearly 1,200 patients enrolled in the Leiden early arthritis cohort, van der Woude et al. were able to measure anti-MAA and anti-AGE antibodies and perform statistical analyses looking at the prevalence and co-occurrence of antibodies, associations with genetic risk factors and associations with different phenotypes of disease.[4]

These researchers were able to show that anti-MAA and anti-AGE antibodies exist in patients with seropositive and seronegative RA and, at a lower prevalence, in patients with such conditions as psoriatic arthritis and crystalline arthritis. More specifically, these antibodies help identify a subgroup among patients with seronegative RA who are also positive for HLA-DRB1*03:01, have increased markers of inflammation and have shown some degree of radiographic progression. Although these antibodies are not a panacea, they may help sub-classify patients within disease categories.

In Sum

A great deal remains to be learned about disease pathogenesis, identifying patients at risk for progression of disease and knowing when to intervene in preclinical disease. 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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Not Your Average Case

Difficult-to-treat rheumatoid arthritis

BY JASON LIEBOWITZ, MD

In Brief

During EULAR 2022, Dr. Jacob van Laar took a deep dive into what defines difficult-to-treat rheumatoid arthritis & how to approach these patients.

EULAR 2022 (VIRTUAL)—It is reassuring for patients and physicians when the presentation and treatment of a disease follow the course outlined in medical textbooks. However, the real world is often much more complicated than an idealized scenario, and clinicians must think critically and creatively about how to care for patients with difficult-to-manage disease.

DR. VAN LAAR

At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Jacob M. van Laar, MD, PhD, professor of rheumatology, University Medical Center Utrecht, the Netherlands, provided an instructive lecture on the subject of difficult-to-treat rheumatoid arthritis (RA).

Challenging Conditions

Dr. van Laar began his presentation with a discussion of patient characteristics that may make efficacious treatment of RA challenging. Certain medical comorbidities may cause disease-modifying anti-rheumatic drugs (DMARDs) to be less effective and may increase the risk of adverse drug reactions. Also, medical comorbidities could hamper a clinician's ability to properly grade RA disease activity, leading to inappropriate treatment decisions.

Examples: Data indicate fibromyalgia can be common in patients with severe RA.[1] Obesity can decrease the effectiveness of treatments, worsen subjective measures of disease activity, reduce the likelihood of achieving remission in early disease, reduce the probability of sustained remission and worsen long-term outcomes in RA.

In addition to medical comorbidities, Dr. van Laar described work that has demonstrated a pauci-immune pathotype that can often be seen when synovial biopsies are performed in patients with difficult-to-treat RA. In these patients, the synovitis seems to be driven by stromal cell pathology, and these cells are not affected by the conventional drugs used to treat RA.

What Is Difficult-to-Treat RA?

Before proceeding with his talk, Dr. van Laar helped provide a clear definition of what may constitute difficult-to-treat RA. He noted that patients in this category should have failed to respond to at least two biologic or targeted synthetic DMARDs with different mechanisms of action after having already failed to respond to conventional synthetic DMARDs. Patients with difficult-to-treat RA may also have signs suggestive of active or progressive disease, namely one or more of the following: at least moderate disease activity, as measured by the Clinical Disease Activity Score or other tools; active synovitis on exam; elevated inflammatory markers or new erosive disease on imaging; the inability to taper glucocorticoids to <7.5 mg of prednisone per day; and/or reduction in quality of life. Finally, the management of symptoms should be perceived by patients and/or rheumatologists as problematic.

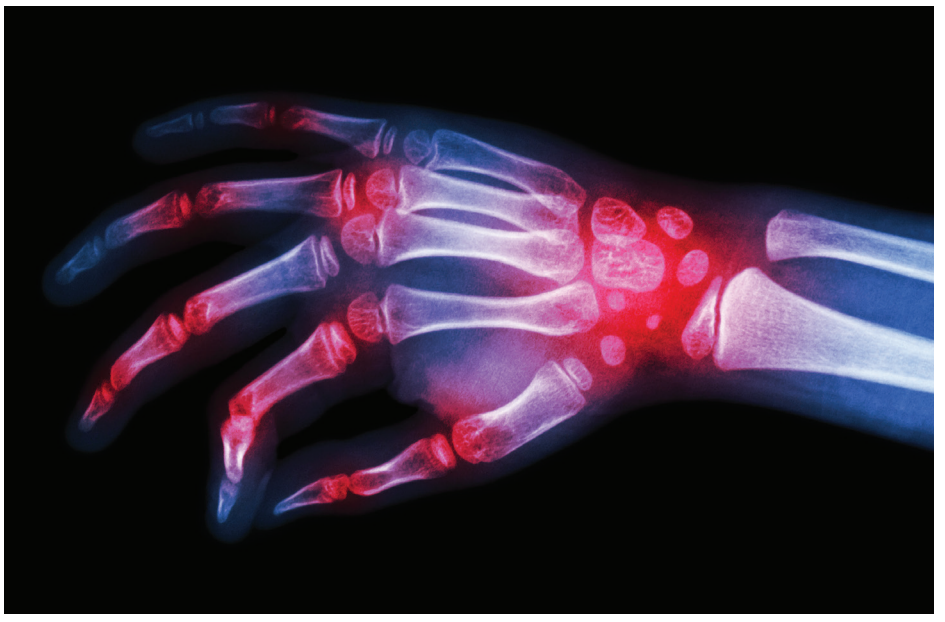
Using this definition of difficult-to-treat RA, 5–20% of all patients with RA may fit into this category.[2]

Contributing Factors

Dr. van Laar discussed work that he and colleagues undertook to better understand the contributing factors and burden of disease seen in patients with difficult-to-treat RA. In this prospective study, 52 patients with RA were classified as having difficult-to-treat disease and compared with 100 patients with RA who did not meet this definition.[3] The authors identified lower socioeconomic status at the onset of RA as an independent risk factor for the development of difficult-to-treat disease.

Other factors that were independently associated with difficult-to-treat disease include limited drug options as a result of adverse events from therapy, mismatch between doctor and patient in the wish to intensify treatment, fibromyalgia and poorer coping skills. A higher prevalence of alcohol use, anxiety and depression was seen in patients with difficult-to-treat disease, compared with controls.

In evaluating the financial aspects of care, patients with difficult-to-treat RA generated about double the healthcare costs of patients without difficult-to-treat disease. The main driver of costs is not just medications, but also the time that family members, friends and relatives invest in caring for these patients. This leads to lost work productivity and collateral costs to these individuals and to society.



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Workflow

A workflow can be used in approaching patients with difficult-to-treat RA. If a patient with RA is showing persistent signs and symptoms of disease activity despite treatment, Dr. van Laar noted the clinician's first step should be to see if the patient meets the EULAR definition of difficult-to-treat disease. The rheumatologist should then assess for comorbidities that can mimic the signs and symptoms of active disease or may interfere with arthritis assessment.

The rheumatologist should also evaluate whether arthritis activity is present, and in some cases where such an assessment is equivocal, use of ultrasound may be indicated. It is also important, in a professional and nonjudgmental way, to speak with the patient and see if medication nonadherence is at play. Once all of these issues have been evaluated and addressed, then changes to pharmacologic treatment can be made while simultaneously increasing focus on nonpharmacological treatments, which include patient education, increased physical exercise and self-management strategies that can help with coping with disease.

Research Agenda

Many questions remain with respect to the research agenda and what is on the horizon for this theme. Potential research questions include: How can clinicians optimally confirm the RA diagnosis in patients with difficult-to-treat disease? What is the role of synovial biopsies in assessing the presence or absence of inflammation in difficult-to-treat disease? Which biologic and targeted synthetic DMARDs may be most effective in treating the majority of these patients? Could the development of the difficult-to-treat state be prevented by adequate management of contributing factors early in the course of disease? How do common issues, such as obesity and smoking, impact these patients long term?

Dr. van Laar explained that because the definition of difficult-to-treat disease has only recently been formalized, much is still to be learned about patients who fit this category. In addition, it is important that research studies use case definitions appropriately so the results may be generalizable to similar patients in the real world.

In Sum

At the end of the lecture, Dr. van Laar stressed the traits, comorbidities and elements of care associated with difficult-to-treat disease are varied and multifactorial, thus a holistic approach to care is important. It is essential to remember that difficult-to-treat disease is not end-stage or irreversible and that creativity, collaboration and good communication with patients are key to helping patients meet their goals. 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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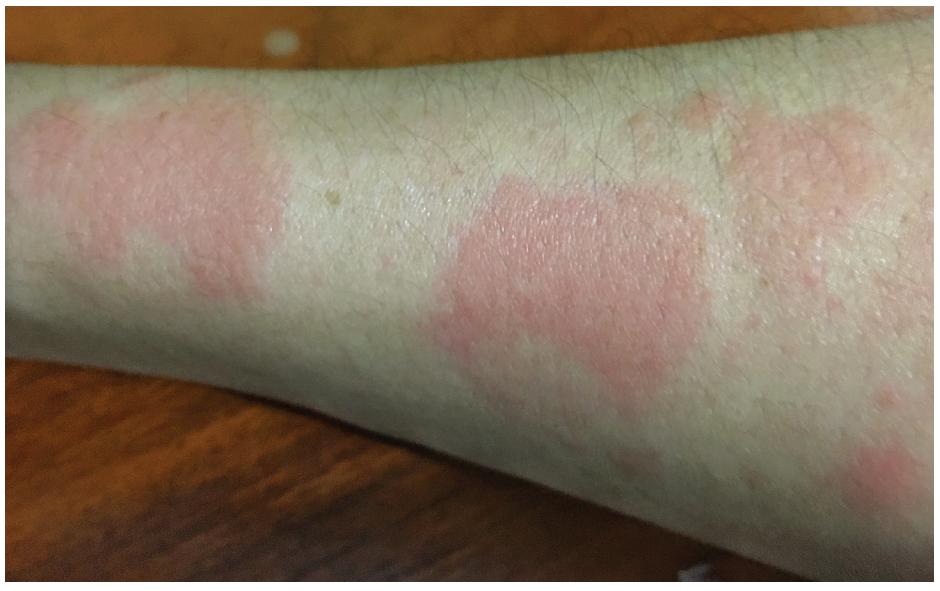
Clinical Challenges in SLE

Glucocorticoids—how much is too much?

■ BY SAMANTHA C. SHAPIRO, MD



‘There’s growing evidence that lower doses of prednisone work well, especially in lupus nephritis.’
—Guillermo Ruiz-Irastorza, MD, PhD

EULAR 2022 (VIRTUAL)—Since its discovery in the 1950s, prednisone has revolutionized our ability to care for patients with rheumatic disease. However, prednisone has two faces—good and evil. And despite a growing array of old and novel therapeutics, prednisone remains a prominent part of care for many patients with systemic lupus erythematosus (SLE).

At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Guillermo Ruiz-Irastorza, MD, PhD, professor of medicine, BioCruces Bizkaia Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Bizkaia, Spain, shared data from his institution regarding its approach to glucocorticoid usage in SLE.

A Patient with Severe SLE

A 52-year-old woman with severe SLE was admitted with acute onset of fever, hemoptysis, bilateral lung infiltrates and hypoxia. One month earlier, she was diagnosed with lupus nephritis class IV and treated with 200 mg of hydroxychloroquine daily, 10 mg of prednisone daily (maximum dose 20 mg) and 500 mg of intravenous cyclophosphamide every 14 days as per the Euro-Lupus protocol, adding 125 mg of methylprednisolone with each cyclophosphamide dose.[1] Bronchoalveolar lavage confirmed diffuse alveolar hemorrhage. Blood cultures grew *Streptococcus pneumoniae*, which was treated with antibiotics.

For treatment of severe SLE, she received 250 mg of intravenous methylprednisolone daily for three days, and rituximab was added to her prior regimen. Her prednisone taper was resumed as per center protocol, with no increase from her pre-flare dose of 10 mg daily. Her oxygenation status improved, and she ultimately achieved a complete renal response.

2 Faces, 2 Mechanisms of Action

Glucocorticoids operate via two separate mechanisms of action: genomic and nongenomic.[2] The genomic effects of glucocorticoids occur when binding to the cytosolic glucocorticoid receptor to induce or inhibit the synthesis of regulator proteins. The genomic mechanism of action is fully active from both an anti-inflammatory and toxic perspective at a 30–40 mg dose of prednisone daily.

On the other hand, the nongenomic effects of glucocorticoids, which don’t induce regulator proteins, occur only at high doses (e.g., 125 mg of prednisone daily, with peak effect at 250–500 mg daily).[2] Nongenomic effects are anti-inflammatory, but nontoxic.

“We could say in a simplistic view that the genomic way is the ‘crappy’ way since patients suffer toxic effects,” Dr. Ruiz-Irastorza explained. “The nongenomic way is the ‘cool’ way in which we have big anti-inflammatory and immunomodulatory effects without the toxicity.”

Pulse doses of glucocorticoids (e.g., 500 mg of intravenous methylprednisolone) are commonly used to treat SLE flares. “We can get maximal anti-inflammatory effects from the genomic and nongenomic pathway by giving these high doses for a short period of time. [And by only using high doses as a short pulse], there’s less time for the toxic genomic effects of glucocorticoids to appear,” Dr. Ruiz-Irastorza said.

Tip of the Iceberg

Most of us are familiar with the SLE iceberg analogy, which depicts disease activity as the tip of the iceberg and damage as the mass of ice below the surface. Studies confirm that damage doesn’t come from active SLE alone; glucocorticoid exposure contributes as well.[3]

In addition, damage as measured by clinical trial damage indices isn’t the only consequence of glucocorticoids. Cosmetic side effects, such as abdominal striae, are also distressing to patients. “These must be taken into consideration since they can result in a high impact on quality of life,” Dr. Ruiz-Irastorza noted.

Can We Use Less?

And now, the million-dollar question: Can we use less glucocorticoids to care for our SLE patients? “There’s growing evidence that lower doses of prednisone work well, especially in lupus nephritis,” said Dr. Ruiz-Irastorza. “Studies show we may even be able to stop glucocorticoids completely in some patients; however, about 20% of these patients will flare, and half of those flares will be severe.”[4]

The 2019 EULAR recommendations for the management of SLE state that “during chronic maintenance treatment, glucocorticoids should be minimized to less than 7.5 mg per day (prednisone equivalent) and, when possible, withdrawn.”[5] However, neither EULAR nor ACR guidelines provide specific instructions on how to taper prednisone, and the use of high-dose oral prednisone (1 mg/kg/day) has become standard for treating moderate to severe lupus activity. Prednisone tapering schedules vary by institution.

“In the last 15 years in our unit,” said Dr. Ruiz-Irastorza, “we’ve been using a slightly different way of tapering glucocorticoids, which we’ve based on three basic principles of action.” These include:

1. Hydroxychloroquine as the cornerstone of SLE treatment for all patients;
2. Maintenance prednisone doses no greater than 5 mg daily; and
3. Pulse doses of methylprednisolone in combination with immunosuppressives at first, with a transition to low-medium glucocorticoid doses that are quickly tapered.

“A patient who’s in ‘clinical remission’ on [maintenance] prednisone 10 mg daily is not actually in clinical remission. We must do whatever it takes to reduce this dose. Until then, we must not consider the patient in remission,” he explained.

Cruces’ Recipe

“Our scheme revolves around brief methylprednisolone pulses,” said Dr. Ruiz-Irastorza. “We believe this approach allows rapid remission with very low toxicity cost to the patient.” By using only brief, high-dose pulses, they aim to maximize the nongenomic effects of glucocorticoids, while avoiding the toxic genomic effects that accrue with longer time on prednisone doses upward of 30 mg daily.

After the methylprednisolone pulses of one to three days’ duration, the prednisone taper starts at a maximum dose of 20–30 mg daily, and is decreased to 5 mg daily by 12 weeks.[6] For example, in an SLE patient with mild-to-moderate disease manifestations (e.g., arthritis, serositis), Dr. Ruiz-Irastorza and colleagues treat with a three-day, 125 mg methylprednisolone pulse, followed by 5–10 mg of prednisone for two to four weeks, and resumption of 5 mg of prednisone daily thereafter.

For major organ manifestations (e.g., lupus nephritis), they treat with a three-day, 250–500 mg methylprednisolone pulse, followed by a fixed prednisone taper scheme that begins at a maximum of 30 mg daily for seven days down to 5 mg daily within 12 weeks. They also administer single 125 mg doses of methylprednisolone every two weeks alongside Euro-Lupus cyclophosphamide dosing.[6]

“The methylprednisolone doses are for increasing the nongenomic effects,

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while decreasing the genomic effects from the oral prednisone taper as quickly as possible," he explained.

Dr. Ruiz-Irastorza continued, "For life-threatening SLE flares, we do almost the same thing, but add rituximab [and/or other agents]. We keep the prednisone tapering scheme the same, and continue to give methylprednisolone pulses with the Euro-Lupus protocol."

Their Evidence

In 2019, Dr. Ruiz-Irastorza et al. published observational data that speaks to the success of their glucocorticoid dosing approach.[7] They compared their SLE cohort with a cohort at the University of Bordeaux and found statistically significant differences in clinical remission on treatment at year one (84% vs. 43%, $P<0.001$), as well as prolonged remission at year one to five (70% vs. 28%, $P<0.001$).

In 2021, they published further observational data regarding the addition of 125 mg of methylprednisolone to the Euro-Lupus protocol for lupus nephritis. Additional methylprednisolone pulses improved complete renal response rates above 80% at 12 months and reduced the need for oral glucocorticoids.[8] Of note, the AURORA 1 trial that led to approval of voclosporin for the treatment of lupus nephritis used a similar prednisone tapering scheme, but achieved lower remission rates.[9]

When Dr. Ruiz-Irastorza et al. compared their patients with historical controls over the last 20 years, they found their glucocorticoid scheme reduced glucocorticoid-related damage and cardiovascular disease without compromising SLE disease control.[10] "Our patients must not pay the price of glucocorticoid toxicity to get SLE well controlled," said Dr. Ruiz-Irastorza. We now have ways to treat the disease in a different manner."

In Sum

Glucocorticoids are a necessary yet toxic component of SLE treatment, and tapering schemes differ by institution and individual prescriber. Dr. Ruiz-Irastorza and colleagues shared captivating data from their experience treating patients with brief methylprednisolone pulses and more rapid, lower dose tapering prednisone schemes. In the future, we hope further studies will confirm the safety and efficacy of this approach and spare our patients from glucocorticoid-related damage. 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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In DISCOVER 1, ACR20 response at Week 24 (primary endpoint)

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

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

†Patients with missing data were considered nonresponders.

Please see full study designs on the following page.

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Infections

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

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

Janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Pre-Treatment Evaluation for Tuberculosis (TB)

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

Immunizations

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

ADVERSE REACTIONS

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

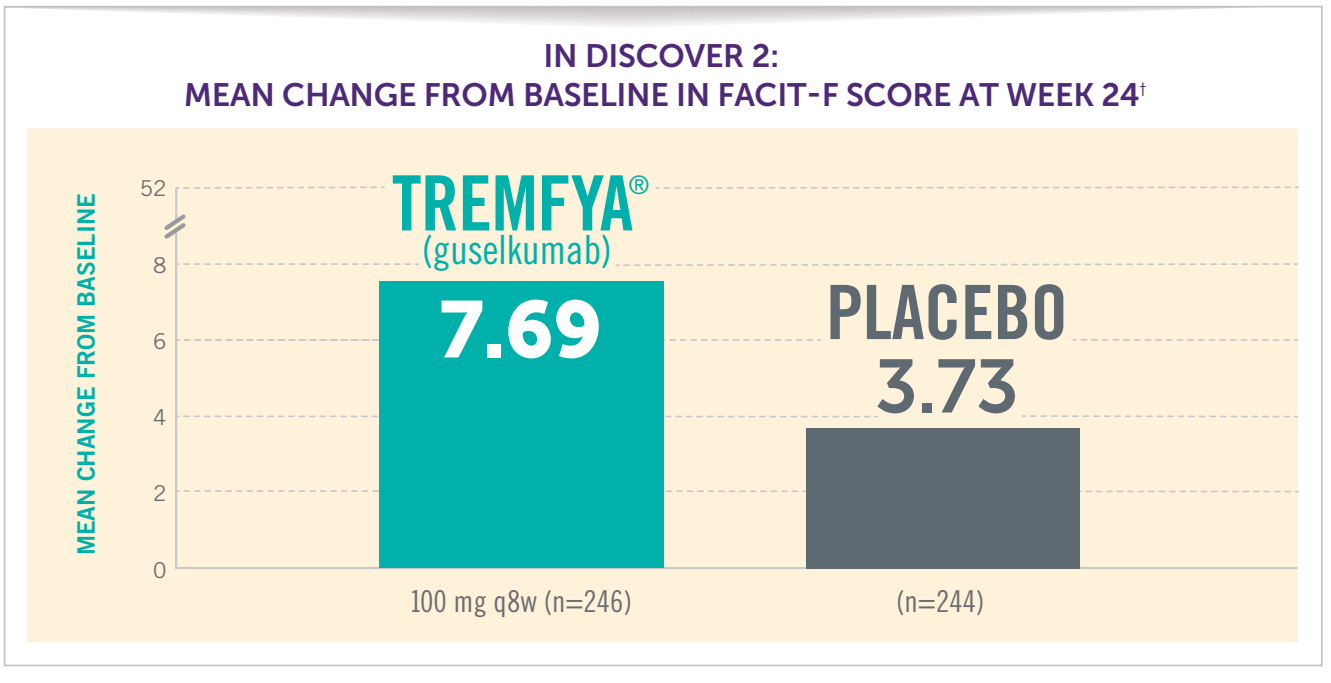
The overall safety profile observed in patients with psoriatic arthritis is generally consistent with the safety profile in patients with plaque psoriasis, with the addition of bronchitis and neutrophil count decreased.

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

cp-82625v3

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

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



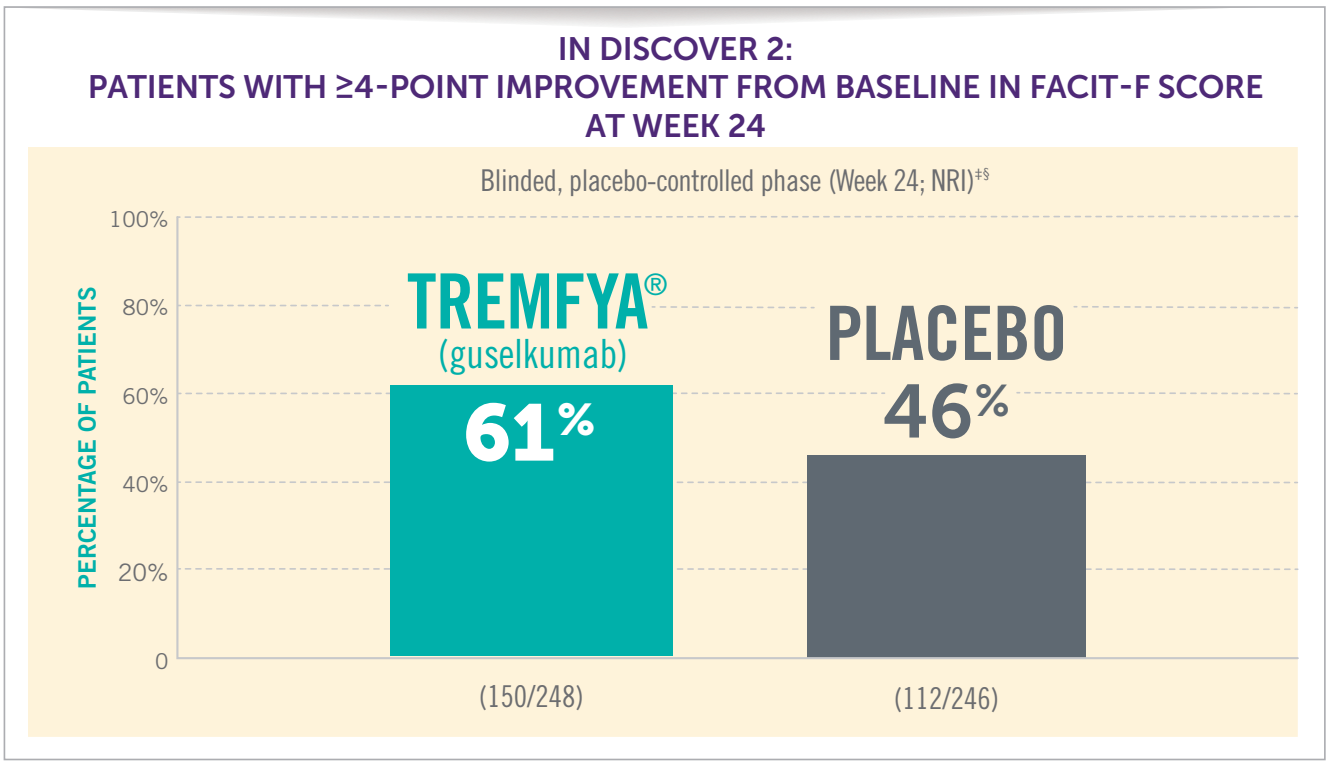
IN DISCOVER 1 AT WEEK 24

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

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

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

≥4 POINT IMPROVEMENT FROM BASELINE IN FACIT-F SCORE



IN DISCOVER 1 AT WEEK 24

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

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

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

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

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

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

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

§Patients with missing data were considered nonresponders.

DEMONSTRATED SAFETY PROFILE[2]

SAFETY PROFILE IN PsA ACROSS 2 CLINICAL TRIALS

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

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

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

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

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

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

VISIT **TREMFYAHCP.COM** TO LEARN MORE

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

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

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

Tremfya® (guselkumab)

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

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

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

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

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

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

bronchitis and neutrophil count decreased. In the 24-week placebo-controlled period, combined across the two studies, bronchitis occurred in 1.6% of subjects in the TREMFYA q8w group and 2.9% of subjects in the TREMFYA q4w group compared to 1.1% of subjects in the placebo group. Neutrophil count decreased occurred in 0.3% of subjects in the TREMFYA q8w and 1.6% of subjects in the TREMFYA q4w group compared to 0% of subjects in the placebo group. The majority of events of neutrophil count decreased were mild, transient, not associated with infection and did not lead to discontinuation. **Immunogenicity:** As with all therapeutic proteins, there is the potential for immunogenicity with TREMFYA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to guselkumab across indications or with the incidences of antibodies to other products may be misleading. Plaque Psoriasis: Up to Week 52, approximately 6% of subjects treated with TREMFYA developed antidrug antibodies. Of the subjects who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing antibodies. Among the 46 subjects who developed antibodies to guselkumab and had evaluable data, 21 subjects exhibited lower trough levels of guselkumab, including one subject who experienced loss of efficacy after developing high antibody titers. Up to Week 156, approximately 9% of subjects treated with TREMFYA developed antidrug antibodies and of these subjects approximately 6% were classified as neutralizing antibodies. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions. Psoriatic Arthritis: Up to Week 24, 2% (n=15) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects, 1 had antibodies that were classified as neutralizing antibodies. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics, efficacy and safety of guselkumab. **Postmarketing Experience:** The following adverse reactions have been reported during post-approval of TREMFYA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to TREMFYA exposure. *Immune system disorders:* Hypersensitivity, including anaphylaxis *[see Warnings and Precautions] Skin and subcutaneous tissue disorders:* Rash *[see Warnings and Precautions]* **DRUG INTERACTIONS CYP450 Substrates:** The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, interferon) during chronic inflammation. Results from an exploratory drug-drug interaction study in subjects with moderate-to-severe plaque psoriasis suggested a low potential for clinically relevant drug interactions for drugs metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 but the interaction potential cannot be ruled out for drugs metabolized by CYP2D6. However, the results were highly variable because of the limited number of subjects in the study. Upon initiation of TREMFYA in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **USE IN SPECIFIC POPULATIONS Pregnancy:** Pregnancy Exposure Registry: There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TREMFYA during pregnancy. Patients should be encouraged to enroll by calling 1-877-311-8972. Risk Summary: There are no available data on TREMFYA use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, TREMFYA may be transmitted from the mother to the developing fetus. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of guselkumab during organogenesis through parturition at doses up to 30 times the maximum recommended human dose (MRHD). Neonatal deaths were observed at 6- to 30-times the MRHD *(see Data)*. The clinical significance of these nonclinical findings is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data: *Animal Data:* In a combined embryofetal development and pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of guselkumab up to 50 mg/kg (30 times the MRHD based on a mg/kg comparison) from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD based on a mg/kg comparison) and three monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD based on a mg/kg comparison). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age. **Lactation:** Risk Summary: There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREMFYA and any potential adverse effects on the breastfed infant from TREMFYA or from the underlying maternal condition. **Pediatric Use:** The safety and efficacy of TREMFYA in pediatric patients (less than 18 years of age) have not been established. **Geriatric Use:** Of the 3406 subjects with plaque psoriasis or psoriatic arthritis exposed to TREMFYA, a total of 185 subjects were 65 years or older, and 13 subjects were 75 years or older. No overall differences in safety or effectiveness were observed between older and younger subjects who received TREMFYA. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **OVERDOSAGE** In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately. **PATIENT COUNSELING INFORMATION** Advise the patient and/or caregiver to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before starting TREMFYA therapy, and each time the prescription is renewed, as there may be new information they need to know. Hypersensitivity Reactions: Advise patients to discontinue TREMFYA and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions]*. Infections: Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions]*. Instruction on Injection Technique: Instruct patients or caregivers to perform the first self-injection under the supervision and guidance of a qualified healthcare professional for proper training in subcutaneous injection technique. Instruct patients who are self-administering to inject the full dose of TREMFYA *[see Medication Guide and Instructions for Use]*. Instruct patients or caregivers in the technique of proper needle and syringe disposal. Needles and syringes should be disposed of in a puncture-resistant container. Advise patients and caregivers not to reuse needles or syringes. Remind patients if they forget to take their dose of TREMFYA to inject their dose as soon as they remember. They should then take their next dose at the appropriate scheduled time.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044
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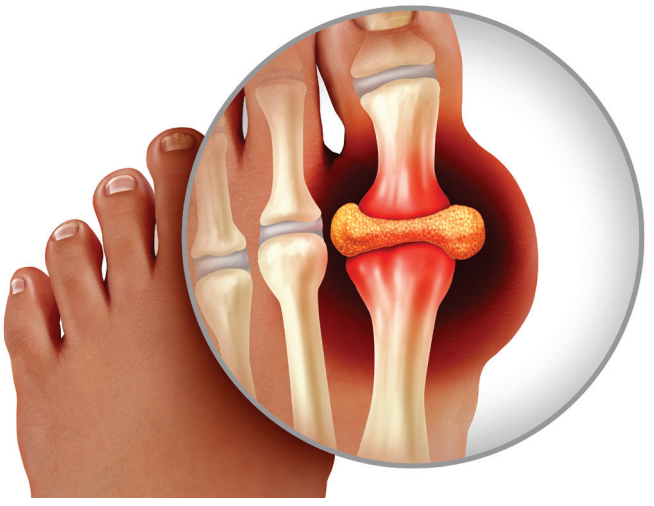
cp-82994v3

Treating to Target in Gout



The trouble with serum urate

■ BY SAMANTHA C. SHAPIRO, MD

EULAR 2022 (VIRTUAL)—*Treat to target* is a familiar phrase in rheumatology. The clinical goals are to minimize and/or abolish symptoms, improve quality of life and improve level of function. So why is treating to target in gout so difficult?

At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Lisa Stamp, MB ChB, FRACP, PhD, DipMus, professor, Department of Medicine, University of Otago, Christchurch, New Zealand, shed light on treating to target in gout.

The Difference

Treating to target in gout differs from other rheumatic diseases. "In rheumatoid arthritis, for example, we target low disease activity (LDA) or remission, and assess this with a composite disease activity score," Professor Stamp explained. "But in gout, we have no widely validated LDA or remission indices. Serum urate concentration has been accepted as the primary outcome measure in clinical trials of urate lowering therapy (ULT) because it allows for smaller, shorter and cheaper randomized controlled trials (RCTs)."

However, a serum urate target has proven problematic, and Professor Stamp proceeded to explain why.

The Controversy

In 2017, the American College of Physicians (ACP) published a Guideline on Management of Acute and Recurrent Gout, which advocated a treat-to-symptom rather than treat-to-target approach for gout management.[1] The ACP determined that "evidence was insufficient to conclude whether the benefits of escalating ULT to reach a serum urate target outweigh the harms associated with repeated monitoring and medication escalation," and "although there is an association between lower urate levels and fewer gout flares, the extent to which the use of ULT to achieve various targets can reduce gout flares is uncertain."

Ultimately, the ACP recommended initiation of ULT only after careful consideration of the benefits, harms and cost. Evidence for monitoring serum urate levels was deemed insufficient and, thus, not recommended either.

"As you can imagine, this caused quite a large amount of consternation amongst the rheumatology community—specifically amongst those who have a real interest in gout management," Professor Stamp said.

What's the Issue?

Why is it so difficult to show that achieving target serum urate improves clinical outcomes in gout? Professor Stamp explained that it takes time for flares and tophi to resolve, and most randomized, controlled trials of ULT have been too short to show benefit. Further, there's been no placebo arm in trials that could highlight the benefit of ULT due to ethical concerns. The paradoxical increase in flares upon starting ULT also complicates the picture.

To illustrate her point, Professor Stamp drew the audience's attention to the 2005 trial published in the *New England Journal of Medicine* demonstrating the effectiveness of febuxostat, compared with allopurinol, for which the primary end point was serum urate less than 6.0 mg per deciliter (mg/dL) at the last three monthly measurements.[2] "Data clearly showed that flares reduced over time," she said, "but even after 12 months, patients were still having flares."

The Evidence

Professor Stamp et al. have worked tirelessly to find evidence to support a treat-to-target approach for gout. The key has been showing that serum urate is an adequate surrogate end point in clinical trials.

In 2018, they published a systematic review and meta-regression analysis of 10 randomized, controlled trials and three open label extension studies.[3] No association was found between the relative risk of gout flare and the difference in proportions of individuals with serum urate less than 6.0 mg/dL in the randomized, controlled trials that had a maximum trial duration of 24 months. However, "based on observational ecological study design data—including longer duration extension studies"—there was an association with reduced gout flares. Further, the duration of ULT was inversely associated with the proportion of patients experiencing flare.

"We decided the next way forward was to use individual patient-level data from two, two-year RCTs. We wanted studies that would be long enough to show a relationship," Professor Stamp continued.

Stamp et al. published results from this work in *Lancet Rheumatology* this past January.[4] They compared serum urate responders (i.e., patients with an average serum urate of less than 6.0 mg/dL between 6 and 12 months post-baseline) with serum urate non-responders (i.e., those with average serum urate greater than 6.0 mg/dL). From the combined individual data from both trials, "significantly fewer serum urate responders had a gout flare than did serum urate non-responders between 12 and 24 months (27% vs. 64%; adjusted odds ratio: 0.29 [95% confidence interval 0.17 to 0.51], $P<0.0001$)." The mean number of flares per patient per month between 12 and 24 months was significantly lower in the serum urate responder group as well.

To summarize, Professor Stamp said, "This study provides evidence that a treat-to-target serum urate approach leads to improved clinical outcomes for our patients."

Experts hope these data will lead to an alignment of gout management recommendations between rheumatology organizations and the ACP. Of note, this evidence was limited by the fact that it relied on post-hoc analysis. But gout experts remain hopeful it will be enough to prompt revision of ACP guidelines.[5]

Professor Stamp was careful to note that "we need to think about more than just serum urate in gout. … Journals are starting to push back against using serum urate as the primary outcome for clinical trials, and it's really interesting to note that the first of these—where gout flares were the primary outcome—was only just published in the *New England Journal of Medicine* in 2022."[6]

What's the Target?

We finally have data to support the use of serum urate as a surrogate outcome measure for gout flares, but what's the most appropriate target level?

To date, no head-to-head trials have compared the current serum urate target of 6.0 mg/dL with lower or higher targets. However, a recent study by Dalbeth et al. examined intensive ULT in patients with erosive gout.[7] Improvement was seen in those with serum urate less than 5 mg/dL as well as 3.4 mg/dL, with no between-group differences. "This data suggests that there is no benefit of a lower target," Professor Stamp said.

Rheumatologists also wonder if the serum urate target should change for patients over time. "For many patients, continuation of treatment in the absence of clinical signs or symptoms is challenging and can carry significant medication burden," said Professor Stamp. "So an alternative strategy would be to induce MSU [monosodium urate] crystal dissolution with a lower target serum urate, and then maintain a state of MSU crystal dissolution with a higher target serum urate after that."

This idea was proposed by Perez-Ruiz et al. in 2011—the so-called "dirty dish" hypothesis, whereby "more is required to get it clean than to keep it clean."[8] Further study is necessary in this regard.

In Sum

We now have increasing evidence from a post-hoc analysis that a serum urate target less than 6.0 mg/dL results in improved clinical outcomes for people with gout. The rheumatology community hopes these data will result in commensurate treat-to-target recommendations for gout management from other professional organizations. However, we still have work to do regarding which serum urate target results in the best clinical outcomes.

"If we cannot define a single target, why should we be treating to target serum urate at all?" Professor Stamp asked. 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.

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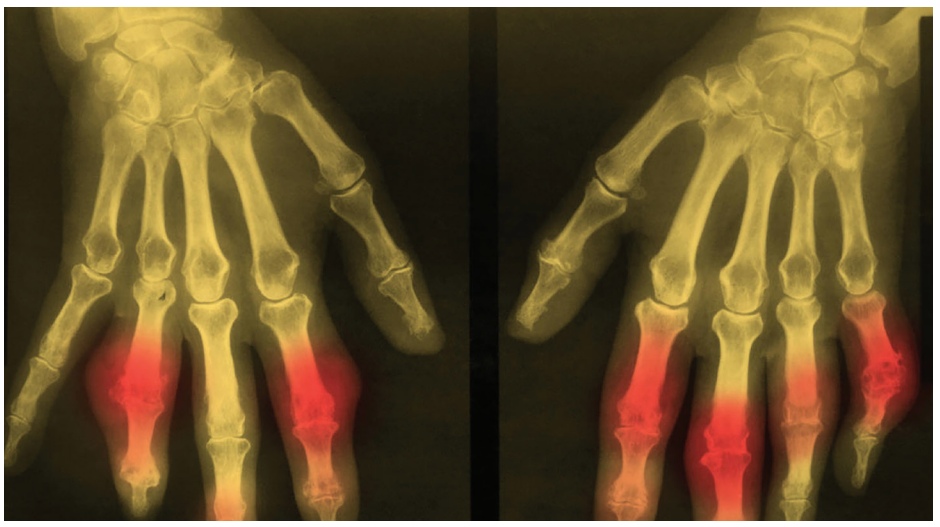
Imaging Modalities in Gout

How to use them in clinical practice

■ BY SAMANTHA C. SHAPIRO, MD



> Dual-energy computed tomography & ultrasound are both more sensitive than plain radiographs & provide noninvasive characterization of monosodium urate crystals with specificity.

EULAR 2022 (VIRTUAL)—For years, the gold standard for gout diagnosis has been the presence of monosodium urate (MSU) crystals on synovial fluid analysis. But any practicing rheumatologist can tell you that tapping a joint isn't always feasible. And any patient with a red, hot, swollen joint can tell you that having a needle stuck into that joint isn't always preferable. Fortunately, imaging is becoming more and more a part of day-to-day gout diagnosis and treatment.

At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Tristan Pascart, MD, PhD, full professor of rheumatology, Université Catholique de Lille, France, provided evidence-based, practical insight into the use of gout imaging modalities in clinical practice.

Diagnosis

In 2015, the ACR and EULAR published classification criteria for gout via a collaborative initiative.[1] The presence of MSU crystals in a symptomatic joint, bursa or tophus was a sufficient criterion for classification as gout. If crystal analysis isn't available, a patient could be classified as having gout via a combination of clinical, laboratory and imaging findings.

However, the criteria aren't 100% sensitive or specific, synovial fluid analysis is invasive and often unavailable, and radiographic gout findings come too late. Additionally, Dr. Pascart noted that "clinical exam and serum urate levels don't reflect the crystal burden in joints, which is why patients flare even after serum urate levels are at goal."

FIGURE 1: USE OF IMAGING FOR GOUT IN CLINICAL PRACTICE

	ULTRASOUND	DUAL-ENERGY COMPUTED TOMOGRAPHY
How?	Look for double contour sign and tophi. Especially useful in early disease (<2 years).	Scan the knees and feet +/- hands. Beware of artifact.
What?	Non-invasive diagnosis and monitoring with high specificity. Varying sensitivity depending on MSU crystal burden.	
When?	At baseline and in follow-up.	
Why?	Flare prognosis. Possibly as a guide for target serum urate—higher MSU crystal burden, lower targets or prolonged prophylaxis?	

Dual-energy computed tomography (DECT) and ultrasound are both more sensitive than plain radiographs and provide noninvasive characterization of MSU crystals with specificity. "This is why imaging findings account for half of the points you need to classify a patient as gout by the ACR/EULAR criteria," Dr. Pascart explained.

Ultrasound

When it comes to ultrasound, the two most important and reliable diagnostic features to look for are the double contour sign and tophi. Both are quite specific for MSU crystals. On the other hand, hyperechoic aggregates have poor inter-observer reliability and insufficient specificity.[2,3] "I wouldn't rely on aggregates alone," Dr. Pascart cautioned.

Ultrasound is also useful as a semi-quantitative tool for monitoring response to treatment. The thickness of the double contour sign can be measured over time. The double contour sign is the ultrasonographic finding that's most sensitive to change.[4]

Like any test, ultrasound has its drawbacks. Dr. Pascart explained, "Ultrasound is observer dependent, and most, if not all, of the data on the diagnostic performance of ultrasound come from expert hands. So we don't really know what happens when less expert people do it."

DECT

When it comes to dual-energy computed tomography, Dr. Pascart noted that "diagnostic accuracy is a bit better for DECT than ultrasound, with the exception of early disease." In early disease (i.e., diagnosis of gout within the first two years of disease onset), ultrasound is more sensitive for new deposits as appreciated by the double contour sign.[5] This is because DECT is limited by resolution. Significant MSU crystal aggregates need to be present to see them.

It's also important to make sure that radiologists aren't counting artifact while calculating MSU crystal burden on DECT images. "Nailbeds have the same signature as MSU crystals and shouldn't be counted. Metal implants can also cause artifact," Dr. Pascart explained.

"I like to use DECT for prognosis and follow-up," Dr. Pascart said, "but I do admit I'm a bit biased since it's so cool. We know there's a relationship between the volume of crystals measured with DECT at baseline and flare risk over the next six months.[6] With ultrasound, after six months of treatment, patients with a greater than 50% decrease in tophus size had less risk of flaring after those six months of treatment.[7] [Given this information], you might argue for a lower serum urate target or prolonged flare prophylaxis if tophus burden as measured by DECT remains high."

Ultrasound & DECT

What about using ultrasound and DECT in combination? Dr. Pascart et al. used prospectively collected data from an outpatient rheumatology clinic to examine the diagnostic accuracy of either modality alone or in combination, by anatomical site (i.e., feet and ankles, and knees).[5] "The general conclusion," Dr. Pascart explained, "was that there was no advantage to combining the two techniques. You gained some sensitivity but lost some specificity."

In Sum

Dr. Pascart concluded his talk with a high-yield summary of the "how, what, when and why" of imaging modalities in gout (see Figure 1, below left). As ultrasound and DECT become more widely available, we can all hope for better care of our gout patients in the future. 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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Refractory Gout Is a Myth

Tips from an expert

BY SAMANTHA C. SHAPIRO, MD

EULAR 2022 (VIRTUAL)—When it comes to inflammatory arthritis, most rheumatology providers would agree that gout is, by far, the most treatable type. However, most patients and primary care providers might disagree. Why the disconnect?

Gout therapies are effective … when properly prescribed. Therein lies the rub. At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Thomas Bardin, MD, rheumatology department, Hôpital Lariboisière, Paris, and professor emeritus, Université de Paris Cité, shared his expertise on refractory gout and whether it should actually exist in 2022.

Definitions & Causes

Refractory gout is defined as the persistence of clinical manifestations of gout due to the inability to reduce the serum urate (SU) concentration below the target 6.0 mg/dL.[1] It's characterized by long disease duration and features of severe disease like frequent flares, polyarticular involvement, tophi, destructive arthropathy and/or chronic inflammatory arthritis. Refractory gout is also associated with many comorbidities and high economic costs.[2,3] The U.S. Food & Drug Administration estimated, when approving pegloticase in 2009, that about 1% of gout patients had refractory disease, but this number is a moving target.[4]

"The cause of refractory gout is obviously mismanagement, and there are multiple sources," Professor Bardin said. Insufficient prescription and dosing of urate-lowering therapy (ULT) remains a major culprit. Poor adherence to therapy results in lack of disease control, which is fueled in part by a general lack of patient and healthcare provider education about gout management. Drug intolerances and contraindications further complicate the picture.[5,6] The list goes on.

Historically, intolerance to allopurinol—mainly due to cutaneous reactions—has been a source of refractory gout. However, Professor Bardin et al. demonstrated the majority of patients with cutaneous intolerance to allopurinol can tolerate febuxostat.[7] He remarked, "Usually I wait for a month [after an allopurinol reaction]—a little longer in the case of drug rash with eosinophilia and systemic symptoms (DRESS)—and start febuxostat at a dose of 40 mg daily, increasing it slowly. In my experience, you can get the patient back to target [SU]."

In the rare cases of patients with skin and/or liver intolerance to both allopurinol and febuxostat, Professor Bardin recommended the use of uricosurics.

ULT Dosing & Chronic Kidney Disease

Many regulatory agencies across the world limit the maximum dosage of allopurinol according to creatinine clearance due to the increased risk of fatal skin reactions. Unfortunately, such restrictions translate into the failure to titrate allopurinol to a dose that reaches SU targets.[8]

In these circumstances, Professor Bardin recommended the use of febuxostat. He explained, "You can use febuxostat in chronic kidney disease (CKD) if the estimated glomerular filtration rate (eGFR) is greater than 30 mL/min/1.73m^2 [because] it's mainly metabolized by the liver."

Febuxostat isn't approved for patients with an eGFR less than 30 mL/min/1.73m^2 because these patients were excluded from pivotal trials. However, data from small series have shown febuxostat can be well tolerated and efficacious in these patients.[9] Professor Bardin shared, "I must say that I do use febuxostat in patients with severe renal failure. I start with a very low dose and slowly increase to target, while closely monitoring the patient."

Professor Bardin noted that the recommendations for gout management in CKD differ between professional organizations (e.g., ACR and EULAR). "But in general, there are ways to deal with this problem, and we can get most of them to an appropriate [SU] target," he said.

When it comes to end-stage renal disease, Professor Bardin reminded us that we've known since the 1960s that "hemodialysis is a good way to manage gout."[10] In addition, renal transplantation used to be a frequent cause of refractory gout due to calcineurin inhibitors causing hyperuricemia, and azathioprine barring the concomitant use of xanthine oxidase inhibitors. "But that problem has now been solved by mycophenolate mofetil, [which is safe to use in combination with allopurinol]," he added.[11]

Flare Prophylaxis

Flare prophylaxis is a crucial and oft-overlooked component of gout care. However, comorbidities like CKD and type 2 diabetes mellitus can complicate drug selection. Colchicine, non-steroidal anti-inflammatory drugs and prednisone may all be contraindicated or undesirable options for certain patients.

Professor Bardin offered, "In patients who cannot be prescribed typical medications for flare prophylaxis, consider canakinumab. It's not approved for [this indication], but has a long duration of action. ULT could be introduced and optimized after one canakinumab dose, which can remain effective up to one year."[12] Additional options might include other interleukin (IL) 11 inhibitors (e.g., anakinra) or tocilizumab in the instance of IL-1 blockade failure.[13,14]

Comorbidities

Last, Professor Bardin pointed out that most gout patients have comorbidities, and we can use several of their other medications to help reduce hyperuricemia. In hypertension, losartan and calcium channel blockers are uricosuric.[15] In hyperlipidemia, fenofibrate lowers SU and may reduce gout attacks.[16] Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to significantly decrease SU levels, and many drugs in this class have multiple indications (e.g., type 2 diabetes mellitus, CKD with albuminuria, heart failure).[17]

Refractory Gout: Myth

Professor Bardin said, "Refractory gout should be prevented and shouldn't exist. Difficult-to-treat gout is not refractory gout. And severe gout is not always refractory."

To illustrate his point, Professor Bardin shared data from his experiences treating gout in Vietnam. "When we introduced EULAR treatment recommendations at one center in Vietnam," he said, "we looked at the first 100 severe gout patients with no previous ULT and no renal failure. To achieve target SU, we had to use a mean allopurinol dose of 520 mg +/-165 mg per day. It was striking to see how life changing allopurinol was for these patients. Flares disappeared, tophi decreased, and quality of life and level of function improved."

In Sum

Over the past decade, major advances in gout care have truly rendered refractory gout a myth. Standard gout therapies like allopurinol and febuxostat—when properly prescribed and taken—are effective for most patients.

Patient and provider education is paramount to gout management success. In tougher cases, we have more options than we did previously, and hyperuricemia can be reduced via medications for comorbidities. Professor Bardin concluded, "I really believe that refractory gout is neglected gout and shouldn't be seen anymore." R

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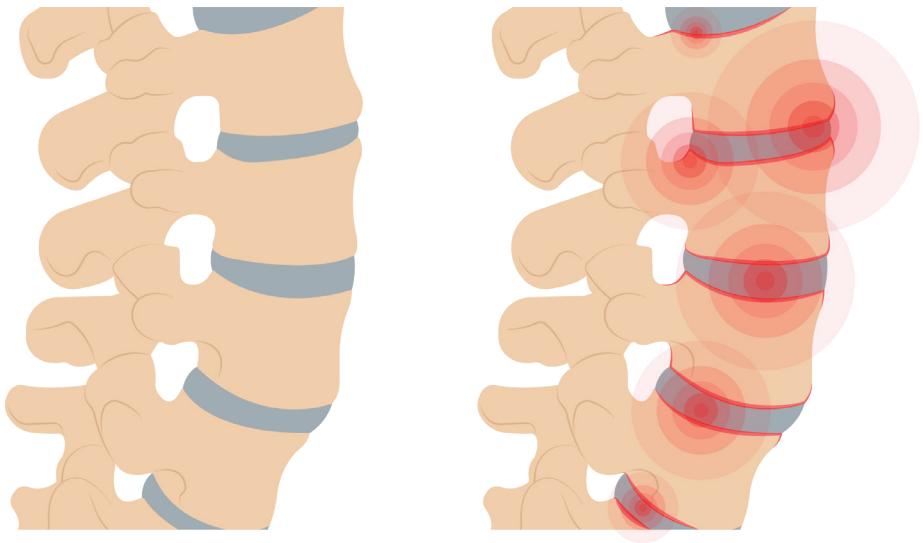
Spine School

Axial manifestations of psoriatic arthritis

BY JASON LIEBOWITZ, MD



DR. HELLIWELL

EULAR 2022 (VIRTUAL)—Psoriatic arthritis (PsA) is known for its ability to affect patients in many domains and manifest with enthesitis, uveitis, dactylitis and peripheral synovitis. At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Philip Helliwell, MA, PhD, DM, FRCP, professor of clinical rheumatology at the University of Leeds and honorary consultant rheumatologist for the Bradford Hospitals NHS Trust, Leeds, England, discussed the importance of recognizing the axial manifestations of this disease and treating these symptoms.

In the original classification of Moll and Wright, the spondyloarthritides included such conditions as ankylosing spondylitis, PsA, reactive arthritis, Behçet's disease, arthritis associated with inflammatory bowel disease (IBD) and Whipple's disease.[1] These conditions shared many features, including sacroiliitis, asymmetric large joint arthritis, inflammation of the bowel, iritis, mucocutaneous ulcerations and erythema nodosum.

A number of years later, Dr. Helliwell, along with Dr. Wright, published a new classification set that eliminated Behçet's disease and Whipple's disease as part of this cadre and added unclassified spondyloarthritis.[2] These concepts of disease continue to evolve, and the distinctions between diseases have been refined, helping clinicians separate patients into more specific subtypes.

Radiographic Features

Dr. Helliwell went on to describe work he published in the 1990s on the differing radiographic features of axial disease seen in various forms of spondyloarthritis. Whereas the sacroiliitis of ankylosing spondylitis and IBD was noted to typically be severe and symmetrical, conditions like PsA and reactive arthritis were found to often be associated with unilateral or bilateral asymmetrical sacroiliitis. Comparing ankylosing spondylitis and IBD with PsA and reactive arthritis, the former were more frequently associated with symphysis, osteoporosis, lumbar straightening, apophyseal joint involvement, bridging syndesmophytes and ligamentous ossification.[3]

Not only do radiographic differences exist between PsA and other conditions with axial disease, but in PsA the clinical presentation of axial disease less often includes classical features of inflammatory back pain.

Dr. Helliwell explained that inflammatory back pain includes pain in the hips or buttocks that improves with activity and worsens with rest, occurs at night, is responsive to non-steroidal anti-inflammatory drugs and involves at least 30 minutes of morning stiffness.

A study by Feld et al. notes that axial involvement in PsA can often be asymptomatic, with only about 45% of patients with PsA and axial disease in this study reporting inflammatory back pain symptoms.[4]

Genetics & Phenotypes

Dr. Helliwell also described the interesting genetics of PsA. The HLA-C:06:02 allele is associated with the highest genetic risk of psoriasis, compared with the HLA-B27, HLA-C12–HLA-B38, and HLA-C06–HLA-B57 haplotypes, which are also associated with PsA. Interestingly, the prevalence of HLA-B27 in PsA is much lower than that seen in ankylosing spondylitis, with prevalence of 20% vs. 80%, respectively.

In the axial form of PsA, the HLA-B27:05:02 allele is associated with symmetrical sacroiliitis, and the HLA-B:08:01–HLA-C:07:01 haplotype is associated with asymmetric sacroiliac involvement.[5]

Putting all of this information together, Dr. Helliwell posited that two phenotypes of axial inflammatory arthritis exist: the classical phenotype and the alternative phenotype. Dr. Helliwell further opined that the majority of patients with axial spondyloarthritis will tend to demonstrate the classical phenotype of disease, but the majority of patients with axial involvement in PsA will demonstrate the alternative phenotype. He explained that such distinctions are essential for clinicians to make because this helps with proper classification of disease and selection of appropriate treatment for patients. (*Editor's note:* For more on this topic, see "Axial Disease in Psoriatic Arthritis," **https://www.the-rheumatologist.org/article/axial-disease-in-psoriatic-arthritis**.)

Treatments

When treatment options are considered, it is important to note that axial disease has not been assessed in most randomized clinical trials of PsA, and thus it has been challenging to create evidence-based recommendations for this manifestation.

Several reasons exist for the absence of clinical trials of axial disease in PsA. These reasons include lack of a validated definition of axial involvement in PsA, lack of a validated outcome measure for the assessment of treatment, the fact that a minority of patients in PsA clinical trials have axial involvement, leading to underpowered assessment of this domain, and the cost and time associated with the serial radiographs and magnetic resonance imaging studies that would be needed to comprehensively assess disease.

Dr. Helliwell did cite a phase 3b study from Baraliakos et al. that evaluated the effect of secukinumab in patients with PsA and axial manifestations. In this double-blind, placebo-controlled, multi-center trial, nearly 500 patients were randomized to receive 300 mg of secukinumab, 150 mg of secukinumab or placebo weekly for four weeks and then every four weeks thereafter for 52 weeks. Patients receiving the 300 mg and 150 mg doses of secukinumab showed significantly improved Assessment of SpondyloArthritis International Society 20 (ASA20) responses at week 12 compared with patients receiving placebo.[6]

Because secukinumab is an inhibitor of interleukin (IL) 17A and this interleukin is closely linked to the actions of IL-23, it is reasonable to ask if IL-23 inhibition would also be effective in treating axial involvement in PsA. However, Dr. Helliwell noted that studies on IL-23 inhibition have demonstrated less successful results, perhaps because it has been shown that cells in the spine are capable of producing IL-17 without IL-23. He did indicate, however, that more studies on IL-23 and IL-12 inhibition may be warranted to see if groups of patients could benefit from such treatments.

In Sum

Dr. Helliwell concluded his lecture with a few take-home points: 1) Heterogeneity of axial involvement in PsA exists, and both the classical and alternative phenotypes of axial disease should be kept in mind; 2) such heterogeneity may relate at least in part to the presence or absence of the HLA-B27 allele; and 3) further studies are needed to define axial PsA and to determine treatment responses in patients with the alternative phenotype of disease. It is through such studies, Dr. Helliwell noted, that his conception of the classical vs. alternative phenotypes of axial disease in PsA and other spondyloarthritic conditions can best be assessed as a conceptual framework. 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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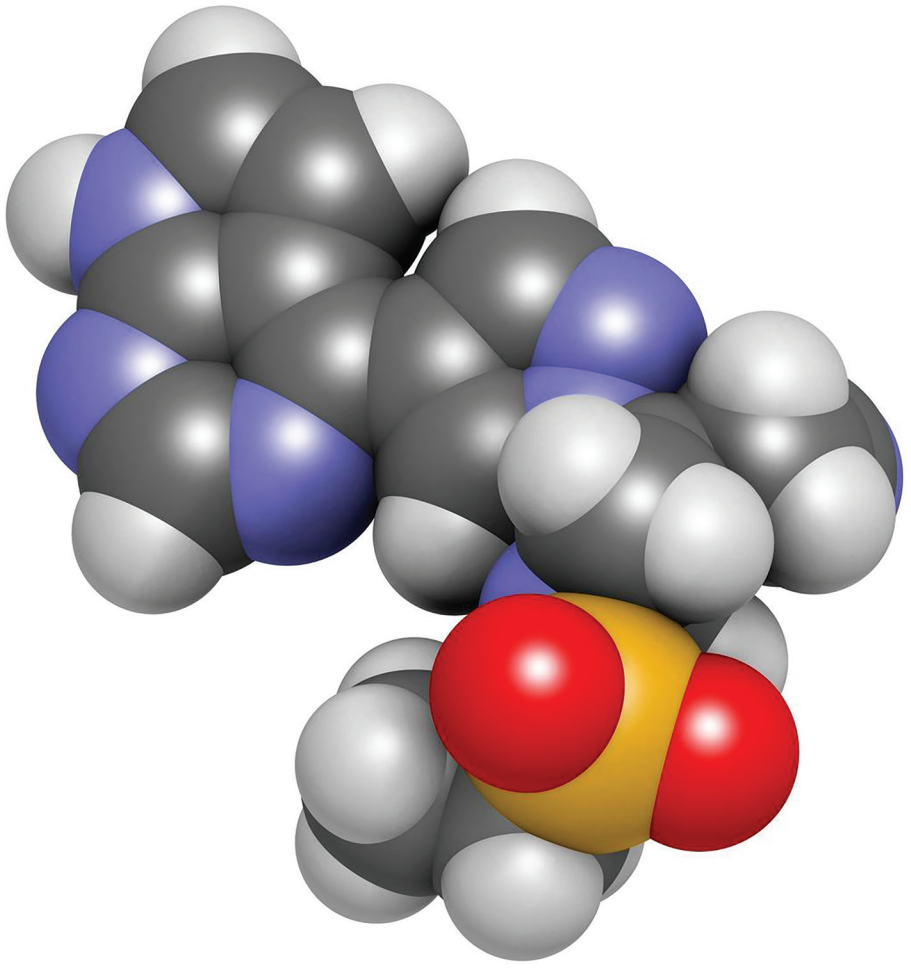
JAK Inhibitors

Are all promises fulfilled?

■ **BY SAMANTHA C. SHAPIRO, MD**



EULAR 2022 (VIRTUAL)—It's been 10 years since the first Janus kinase (JAK) inhibitor was approved for the treatment of rheumatoid arthritis (RA) in the U.S., with several others following suit. Hopes were high for JAK inhibitors to revolutionize RA care. So were all promises fulfilled?

At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Hendrik Schulze-Koops, MD, PhD, professor, Division of Rheumatology and Clinical Immunology, Ludwig-Maximilians University Munich, Germany, reviewed the data available to answer this question. He focused on JAK inhibitors as a class, as opposed to specific drugs.

JAK Inhibitor Promises

Dr. Schulze-Koops first delineated promises of JAK inhibitor therapies with help from an ACR Convergence 2021 abstract.[1] Taylor et al. conducted surveys to understand why physicians chose JAK inhibitors for certain patients. The most important clinical reason for a physician to prescribe a JAK inhibitor was the hope for strong overall efficacy. This was followed by a desire for a fast onset of action, inhibition of disease progression, strong efficacy as monotherapy and achievement of clinical remission.

Consequently, Dr. Schulze-Koops organized his talk by four JAK inhibitor promises: 1) efficacy; 2) drug survival; 3) safety; and 4) simple mechanism of action.

Promise 1: Efficacy

"Some years ago, it was very apparent that whatever we did with biologics, we had similar ACR20, ACR50, and ACR70 responses across the available biologic disease-modifying anti-rheumatic drugs (bDMARDs). Whether it was tumor necrosis factor-α (TNFα) inhibitors or a non-TNFα inhibitor, we were seeing about a 60–70% ACR20, 30% ACR50 and 20% ACR70 response rates. This is what the JAK inhibitors had to compete with," Dr. Schulze-Koops explained.[2]

In 2012, we saw data showing an ACR20 response rate of 59.8% at month three for a JAK inhibitor as monotherapy.[3] A year later, we saw data speaking to the efficacy of a JAK inhibitor in combination with methotrexate in patients with moderate-to-severe RA who had failed to respond to TNFα inhibitors. The ACR20 response rate was 41.7% at month three, with a small percentage of patients even achieving Disease Activity Score-28 (DAS28) remission.[4]

In 2017, a year-long study demonstrated that a JAK inhibitor in combination with methotrexate worked quickly and better than a TNFα inhibitor, with an increased ACR20 response rate at month three with the JAK inhibitor vs. adalimumab (70% vs. 61%, *P*=0.014). Responses were maintained for at least a year.[5]

However, Dr. Schulze-Koops noted that "only about 15% of patients reached the treatment goal that we have given ourselves for RA [low disease activity or remission] in these trials."[3,5]

"I would say that in RA, JAK inhibitors are at least as effective as other bDMARDs in terms of clinical response in methotrexate and TNFα inhibitor non-responder populations," he concluded. "The promise that they're as good as bDMARDs is fulfilled, but a promise *beyond* that—100% remission—is not fulfilled."

Promise 2: Drug Survival

Dr. Schulze-Koops next addressed JAK inhibitor drug survival (i.e., the length of time until discontinuation of drug). Drug survival considers discontinuation for all reasons (e.g., tolerability, side effects, safety, effectiveness). "The half-life of TNFα inhibitor therapy is about two years because these drugs lose their effect and patients become secondary non-responders," he said. "On the other hand, the half-life of JAK inhibitors is close to five years. So I would say that promise no. 2 is fulfilled."[6,7]

Promise 3: Safety

Since JAK inhibitor development, numerous attempts have been made to document the safety of JAK inhibitors for patients, and an enormous amount of data exist from which to deduce safety statements. Studies have pooled data from phase 1, 2, 3 and 3B/4 randomized controlled trials (RCTs) and open-label, long-term extension studies.

Initial long-term safety data indicated that safety profiles were generally comparable between JAK inhibitors and bDMARDs. "Tofacitinib and baricitinib fell almost in the middle when it came to problems we detect with bDMARDs, with the exception of [an increased rate] of the incidence of herpes zoster," Dr. Schulze-Koops remarked.[8,9]

Regarding major adverse cardiovascular events (MACE), a 2019 systematic review and meta-analysis of 26 RCTs didn't demonstrate an increased risk of MACE with JAK inhibitors over placebo.[10] Recent observational data from RABBIT, the German register for the long-term observation of therapy with biologics in adult patients with RA, also didn't demonstrate an increased incidence rate of MACE compared with TNFα inhibitors or conventional synthetic DMARDs.[11] This held true for a higher risk group of patients aged 50 and above with one or more cardiovascular risk factors.

Finally, a 2020 systematic review and meta-analysis of 82 studies comprising 66,159 patients with immune-mediated diseases (inflammatory bowel disease, RA, psoriatic arthritis and ankylosing spondylitis) didn't demonstrate an increased risk of malignancy or MACE, either.[12]

"Based on these studies, the JAK inhibitors have a benign safety profile that wouldn't put our patients at a particular risk—except for herpes zoster, which we can manage these days by vaccination," Dr. Schulze-Koops remarked. However, we all now know about the ORAL surveillance study, which has changed things."

The ORAL surveillance study was published in the *New England Journal of Medicine* in January 2022. This was a "randomized, open-label, noninferiority, post-authorization, safety end-point trial involving patients with active RA despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor."[13]

Dr. Schulze-Koops explained, "The ORAL investigators intentionally looked at an 'at-risk population.' And all of a sudden it appeared there was an increased risk of MACE and malignancy compared with TNFα inhibitors."

Shortly after the publication of ORAL, another study (STAR-RA) showed similar results.[14] STAR-RA looked at two cohorts of RA patients initiating therapy with tofacitinib or a TNFα inhibitors: "a real-world evidence cohort consisting of routine care patients, and an RCT-duplicate cohort mimicking inclusion and exclusion criteria from the ORAL surveillance trial to calibrate results against the trial findings."

"The real-world experience cohort had no increased risk for cardiovascular outcomes," explained Dr. Schulze-Koops, "similar to our RABBIT register data." However, tofacitinib was associated with an

continued on page 53

The most important clinical reason for a physician to prescribe a JAK inhibitor was the hope for strong overall efficacy.

MOLEKUUL / SCIENCE SOURCE

For adults with active psoriatic arthritis (PsA)[1]

#1 PRESCRIBED BIOLOGIC IN **NEW AND SWITCHING** PLAQUE PSORIASIS PATIENTS[2]*

*As of 10/2021. New patients defined as bio-naïve; switch patients defined as bio-experienced switching biologics. Source: Integrated Symphony Health (PatientSource) and IQVIA (NSP) through proprietary method on diagnosis classification.

NOTHING IS EVERYTHING

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

For your PsA patients, that's everything.

INDICATIONS[1]

Psoriatic Arthritis: SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

Plaque Psoriasis: SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

SAFETY CONSIDERATIONS[1]

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of its excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately. SKYRIZI may increase the risk of infection.

Instruct patients to report signs or symptoms of clinically important infection during treatment. Should such an infection occur, discontinue SKYRIZI until infection resolves. Evaluate patients for tuberculosis infection prior to initiating treatment with SKYRIZI. Avoid use of live vaccines in SKYRIZI patients.

Please see additional Important Safety Information and the Brief Summary of full Prescribing Information on adjacent pages of this advertisement.

Skyrizi®
risankizumab-rzaa

JOINT EFFICACY

SKYRIZI met its primary endpoint (ACR20 at Week 24) in 2 clinical trials.[1]

ACR20/50/70, complete resolution of enthesitis/dactylitis, and minimal disease activity at Week 24 with results up to ~1 year in **PsA.**[1,3,4†]

SKIN CLEARANCE

PASI 90 response vs placebo at Week 24 with response rates at 1 year in **PsA.**[3-6†]

WELL-STUDIED SAFETY PROFILE

Evaluated in 21 clinical trials (4 **PsA,** 17 **Ps**). The safety profile in **PsA** is generally consistent with the safety profile of patients with **Ps.**[1,7‡]

EXCEPTIONAL ACCESS & SUPPORT

>95% of commercial and Medicare Part D patients have preferred 1L TIM coverage.[8§‖]

- National commercial and Medicare Part D formulary coverage under the pharmacy benefit as of July 2022.

Skyrizi Complete provides exceptional 1:1 patient support.

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

THE ONLY PEN
FOR PsA AND Ps WITH
4 INJECTIONS A YEAR
AFTER 2 INITIATION DOSES[1]

Scan this QR code or visit SkyriziHCP.com/rheumatology to learn more about SKYRIZI for PsA

STUDY DESIGNS

KEEPsAKE 1 (N=964) and **KEEPsAKE 2** (N=443) were 2 randomized, double-blind, placebo-controlled studies that evaluated the efficacy and safety of SKYRIZI 150 mg vs placebo over 24 weeks with a long-term open-label extension for up to an additional 204 weeks. Both studies enrolled adult subjects with **active psoriatic arthritis**. In KEEPsAKE 1, the study population had an inadequate response or intolerance to at least 1 csDMARD; while in KEEPsAKE 2, patients had an inadequate response or intolerance to at least 1 biologic therapy OR to at least 1 csDMARD.[1]

‡Includes 4 PsA Phase 2-3 studies (including KEEPsAKE 1 and KEEPsAKE 2). Includes 17 Phase 1-3 studies in Ps encompassing 5 trials using integrated data evaluated at Week 16 (including UltIMMa-1, UltIMMa-2, IMMhance, and IMMVent) and 12 additional trials, including LIMMitless.[7]

§Formulary definitions: Preferred means the product is placed on the plan's preferred formulary. Preferred may include the lowest copay or coinsurance tier.

‖Coverage requirements and benefit designs vary by payer and may change over time. Please consult with payers directly for the most current reimbursement policies.

1L=first-line; ACR=American College of Rheumatology; csDMARD=conventional synthetic disease-modifying antirheumatic drug; OLE=open-label extension; PASI=Psoriasis Area and Severity Index; Ps=psoriasis; TIM=targeted immunomodulator; TNFi=tumor necrosis factor inhibitor.

Skyrizi®
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INDICATIONS[1]

Psoriatic Arthritis: SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

Plaque Psoriasis: SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

IMPORTANT SAFETY INFORMATION[1]

Hypersensitivity Reactions

SKYRIZI® (risankizumab-rzaa) is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately.

Infection

SKYRIZI may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Tuberculosis (TB)

Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating SKYRIZI, complete all age appropriate vaccinations according to current immunization guidelines.

Adverse Reactions

Most common (≥1%) adverse reactions associated with SKYRIZI include upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections.

In psoriatic arthritis phase 3 trials, the incidence of hepatic events was higher with SKYRIZI compared to placebo.

SKYRIZI is available in a 150 mg/mL prefilled syringe and pen.

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

References: 1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **2.** Data on file, AbbVie Inc. In-play patient share. January 2021. **3.** Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from KEEPsAKE 1. Poster presented at: 2021 Fall Clinical Dermatology Conference (FC21) Hybrid Meeting; October 21-24, 2021; Las Vegas, Nevada. **4.** Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from KEEPsAKE 2. Poster presented at: 2021 Fall Clinical Dermatology Conference (FC21) Hybrid Meeting; October 21-24, 2021; Las Vegas, Nevada. **5.** Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1. *Ann Rheum Dis.* 2022;81(2):225-231. doi:10.1136/annrheumdis-2021-221019 **6.** Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2. *Ann Rheum Dis.* 2022;81(3):351-358. doi:10.1136/annrheumdis-2021-221048 **7.** Gordon KB, Blauvelt A, Bachelez H, et al. Long-term safety of risankizumab in patients with psoriatic disease: findings from integrated analyses of 17 clinical trials in psoriasis and 4 in psoriatic arthritis. Presented at American Academy of Dermatology Annual Meeting; March 25-29, 2022. **8.** Data on file, AbbVie Inc. July 2022.

Scan this QR code or visit SkyriziHCP.com/rheumatology to learn more about SKYRIZI for PsA

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US-SKZR-220124 August 2022

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SKYRIZI® (sky-RIZZ-ee) (risankizumab-rzaa) injection, for subcutaneous use
150 mg/mL single-dose pen and prefilled syringe
600 mg/10 mL single-dose vial
360 mg/2.4 mL single-dose prefilled cartridge with on-body injector

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Plaque Psoriasis

SKYRIZI® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis

SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

Crohn's Disease

SKYRIZI is indicated for the treatment of moderately to severely active Crohn's disease in adults.

CONTRAINDICATIONS

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately *[see Adverse Reactions]*.

Infections

SKYRIZI may increase the risk of infections *[see Adverse Reactions]*.

Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the PsO-3 study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Hepatotoxicity in Treatment of Crohn's Disease

A serious adverse reaction of drug-induced liver injury was reported in a patient with Crohn's disease (ALT 54x ULN, AST 30x ULN, and total bilirubin 2.2x ULN) following two intravenous doses of SKYRIZI 600 mg in conjunction with a rash that required hospitalization. The liver test abnormalities resolved following administration of steroids. SKYRIZI was subsequently discontinued.

For the treatment of Crohn's disease, evaluate liver enzymes and bilirubin at baseline, and during induction at least up to 12 weeks of treatment. Monitor thereafter according to routine patient management.

Consider other treatment options in patients with evidence of liver cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Tuberculosis *[see Warnings and Precautions]*
- Hepatotoxicity in Treatment of Crohn's disease *[see Warnings and Precautions]*

Clinical Trials Experience

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

Plaque Psoriasis

A total of 2234 subjects were treated with SKYRIZI in clinical development trials in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled trials were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical trials.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis

[b] Includes: headache, tension headache, sinus headache, cervicogenic headache

[c] Includes: fatigue, asthenia

[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth

[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared with 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis, and herpes zoster. In Studies PsO-1 and PsO-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety Through Week 52

Through Week 52, no new adverse reactions were identified, and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

Psoriatic Arthritis

The overall safety profile observed in subjects with psoriatic arthritis treated with SKYRIZI is generally consistent with the safety profile in subjects with plaque psoriasis. Additionally, in the Phase 3 placebo-controlled trials the incidence of hepatic events was higher in the SKYRIZI group (5.4%, 16.7 events per 100 patient years) compared to the placebo group (3.9%, 12.6 events per 100 patient years). Of these, the most common events that were reported more frequently in both the placebo group and the SKYRIZI group were ALT increased (placebo: n=12 (1.7%); SKYRIZI: n=16 (2.3%)), AST increased (placebo: n=9 (1.3%); SKYRIZI: n=13 (1.8%)), and GGT increased (placebo: n=5 (0.7%); SKYRIZI: n=8 (1.1%)). There were no serious hepatic events reported. The incidence of hypersensitivity reactions was higher in the SKYRIZI group (n=16, 2.3%) compared to the placebo group (n=9, 1.3%). In the Phase 3 placebo-controlled trials, hypersensitivity reactions reported at a higher rate in the SKYRIZI group included rash (placebo: n=4 (0.6%); SKYRIZI: n=5 (0.7%), allergic rhinitis (placebo: n=1 (0.1%); SKYRIZI: n=2 (0.3%), and facial swelling (placebo: n=0 (0.0%); SKYRIZI n=1 (0.1%). One case of anaphylaxis was reported in a subject who received SKYRIZI in the Phase 2 clinical trial.

Crohn's Disease

SKYRIZI was studied up to 12 weeks in subjects with moderately to severely active Crohn's disease in two randomized, double-blind, placebo-controlled induction studies (CD-1, CD-2) and a randomized, double-blind, placebo-controlled, dose-finding study (CD-4; NCT02031276). Long-term safety up to 52 weeks was evaluated in subjects who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (CD-3).

In the two induction studies (CD-1, CD-2) and the dose finding study (CD-4), 620 subjects received the SKYRIZI intravenous induction regimen. In the maintenance study (CD-3), 142 subjects who achieved clinical response defined as a reduction in CDAI of at least 100 points from baseline after 12 weeks of induction treatment with intravenous SKYRIZI in studies CD-1 and CD-2, received SKYRIZI subcutaneously as a maintenance regimen.

Adverse reactions reported in > 3% of subjects in induction studies and at a higher rate than placebo are shown in Table 2.

Table 2. Adverse Drug Reactions Reported in > 3% of Subjects with Crohn's Disease Treated with SKYRIZI in Placebo-Controlled 12-Week Induction Studies

Adverse Drug Reactions	SKYRIZI 600 mg Intravenous Infusion[a] N = 620 n (%)	Placebo N = 432 n (%)
Upper respiratory infections[b]	66 (10.6)	40 (9.3)
Headache[c]	41 (6.6)	24 (5.6)
Arthralgia	31 (5.0)	19 (4.4)

[a] SKYRIZI 600 mg as an intravenous infusion at Week 0, Week 4, and Week 8.

[b] Includes: influenza like illness, nasopharyngitis, influenza, pharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, COVID-19, nasal congestion, respiratory tract infection viral, viral pharyngitis, tonsillitis, upper respiratory tract inflammation

[c] Includes: headache, tension headache

Adverse reactions reported in >3% of subjects in the maintenance study and at a higher rate than placebo are shown in Table 3.

Table 3. Adverse Reactions Reported in >3% of Subjects with Crohn's Disease Treated with SKYRIZI in Placebo-Controlled 52-Week Maintenance Study (CD-3)

Adverse Drug Reactions	SKYRIZI 360 mg Subcutaneous Injection[a] N = 142 n (%)	Placebo N = 143 n (%)
Arthralgia	13 (9.2)	12 (8.4)
Injection site reactions[b,c]	8 (5.6)	4 (2.8)
Abdominal pain[d]	12 (8.5)	6 (4.2)
Anemia	7 (4.9)	6 (4.2)
Pyrexia	7 (4.9)	4 (2.8)
Back pain	6 (4.2)	3 (2.1)
Arthropathy	5 (3.5)	2 (1.4)
Urinary tract infection	5 (3.5)	4 (2.8)

[a] SKYRIZI 360 mg at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks

[b] Includes: injection site rash, injection site erythema, injection site swelling, injection site urticaria, injection site warmth, injection site pain, injection site hypersensitivity, injection site reaction

[c] Some subjects had multiple occurrences of injection site reactions. The adverse reaction is included only once per subject.

[d] Includes: abdominal pain, abdominal pain upper, abdominal pain lower

Specific Adverse Drug Reactions

Infections

In the maintenance study (CD-3) through Week 52, the rate of infections was 36.6% (60.8 events per 100 subject-years) in subjects who received SKYRIZI compared to 36.4% (60.3 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction. The rate of serious infections was 5.6% (7.4 events per 100 subject-years) in subjects who received SKYRIZI compared to 2.1% (2.4 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction.

Lipid Elevations

Elevations in lipid parameters (total cholesterol and low-density lipoprotein cholesterol [LDL-C]) were first assessed at 4 weeks following initiation of SKYRIZI in the induction trials (CD-1, CD-2). Increases from baseline and increases relative to placebo were observed at Week 4 and remained stable to Week 12. Following SKYRIZI induction, mean total cholesterol increased by 9.4 mg/dL from baseline to a mean absolute value of 175.1 mg/dL at Week 12. Similarly, mean LDL-C increased by 6.6 mg/dL from baseline to a mean absolute value of 92.6 mg/dL Week 12. Following maintenance treatment with SKYRIZI, mean LDL-C increased by 2.3 mg/dL from baseline to Week 52, to an absolute value of 102.2 mg/dL.

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 in the studies described below with the incidence of antibodies in other studies or to other products, including other risankizumab products, may be misleading.

Plaque Psoriasis

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI) had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

Psoriatic Arthritis

By Week 28, approximately 12.1% (79/652) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had antibodies that were classified as neutralizing. Antibodies to risankizumab-rzaa were not associated with changes in clinical response for psoriatic arthritis. A higher proportion of subjects with anti-drug antibodies experienced hypersensitivity reactions (6.3% (5/79)) and injection site reactions (2.5% (2/79)) compared to subjects without anti-drug antibodies (3.8% (22/574) with hypersensitivity reactions and 0.7% (4/574) with injection site reactions). None of these hypersensitivity and injection site reactions led to discontinuation of risankizumab-rzaa.

Crohn's Disease

By Week 64, approximately 3.4% (2/58) of subjects treated with SKYRIZI at the recommended induction and maintenance dosages developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had antibodies that were classified as neutralizing.

Postmarketing Experience

The following adverse reactions have been reported during post-approval of SKYRIZI. 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 SKYRIZI exposure:

- *Skin and subcutaneous tissue disorders*: eczema and rash

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161 or visiting http://glowpregnancyregistry.com.

Risk Summary

Available pharmacovigilance and clinical trial data with risankizumab use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on risankizumab-rzaa, monoclonal antibodies can be actively transported across the placenta, and SKYRIZI may cause immunosuppression in the in utero-exposed infant**.** There are adverse pregnancy outcomes in women with inflammatory bowel disease *(see Clinical Considerations)*.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 or 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. Increased fetal/infant loss was noted in pregnant monkeys at the 50 mg/kg dose *(see Data)*. The 50 mg/kg dose in pregnant monkeys resulted in approximately 10 times the exposure (AUC) in humans administered the 600 mg induction regimen and 39 times the exposure (AUC) to the 360 mg maintenance doses, respectively. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease is associated with increased disease activity. 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.

Fetal/Neonatal adverse reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because risankizumab may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to SKYRIZI in utero. There are insufficient data regarding infant serum levels of risankizumab at birth and the duration of persistence of risankizumab in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 5 months after birth should be considered because of the half-life of the product.

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition, and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology, or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared with the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg and the NOAEL for developmental toxicity was identified as 5 mg/kg. On an exposure (AUC) basis, the 5 mg/kg dose in pregnant monkeys resulted in approximately 1.24 times the exposure in humans administered the 600 mg induction regimen and 5 times the exposure in humans administered the 360 mg maintenance doses, respectively. In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17%-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Lactation

Risk Summary

There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to risankizumab-rzaa are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

Pediatric Use

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

Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in SKYRIZI exposure, safety, or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

Clinical studies of SKYRIZI for the treatment of Crohn's disease did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

No clinically meaningful differences in the pharmacokinetics of risankizumab-rzaa were observed in geriatric subjects compared to younger adult subjects with Crohn's disease.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hypersensitivity Reactions

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

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions]*.

Hepatotoxicity in Treatment of Crohn's Disease

Inform patients that SKYRIZI may cause liver injury, especially during the initial 12 weeks of treatment. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of liver dysfunction. (e.g., unexplained rash, nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) *[see Warnings and Precautions]*.

Administration of Vaccines

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

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique.

If using SKYRIZI 75 mg/0.83 mL, instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the full 150 mg dose of SKYRIZI.

Instruct patients or caregivers in the technique of pen or syringe disposal.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to SKYRIZI during pregnancy and patients can call 1-877-302-2161 *[see Use in Specific Populations]*.

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Difficult-to-Treat Lupus

When & how to use new therapies

BY SAMANTHA C. SHAPIRO, MD

> Medication regimens for SLE patients can be as heterogeneous as the patients themselves.

EULAR 2022 (VIRTUAL)—Systemic lupus erythematosus (SLE) is a heterogeneous disease, and therapies must be individualized for optimal patient care. In the past few years, we've seen the advent of several new SLE drugs, and older drugs continue to play a role. So where should we start?

At the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR), Martin Aringer, MD, Department of Internal Medicine III, Rheumatology, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Germany, provided practical tips on when and how to use new therapies.

Basic Principles

When it comes to SLE management, Dr. Aringer explained, "We need to get both the inflammatory activity and the glucocorticoid dose down. If we fail in either regard, it's likely the outcome in decades to come won't be very good for the patient."

Additionally, medication selection is only a small part of SLE care. Medication adherence, trust and understanding of disease are paramount. And several situations—like drug intolerances or contraindications, antiphospholipid syndrome, or the desire to have a child—can complicate management. "Every SLE patient is different. It can be any combination [of the above]," Dr. Aringer noted.

Therapeutic Selection

Medication regimens for SLE patients can be as heterogeneous as the patients themselves. Hydroxychloroquine remains the cornerstone of SLE treatment.[1] But when hydroxychloroquine alone fails to control disease, the next best steps aren't clear.

Dr. Aringer advised, "Figure 1 from the 2019 EULAR recommendations for the management of SLE is a good place to start." The figure outlines recommended drugs for the treatment of non-renal SLE based on severity of disease manifestation, with grading of recommendations provided for each drug.[1] For mild to moderate SLE, methotrexate and azathioprine are listed as options. For moderate to severe disease, calcineurin inhibitors, mycophenolate, belimumab, cyclophosphamide and rituximab can also be considered. Newer therapies like anifrolumab and voclosporin aren't included in this figure given the timing of publication.

Options

Newer therapies are exciting, but older drugs still have a place in SLE care. Dr. Aringer noted, "Data show that mycophenolate and azathioprine take a bit of time to work. Peak effect is seen at about 12 months. So if you can be patient, be patient."[2]

Belimumab is approved by the U.S. Food & Drug Administration (FDA) for the treatment of autoantibody-positive SLE and active lupus nephritis patients who are receiving standard therapy. Belimumab can take up to six months to become fully effective, but it may improve fatigue a bit earlier.[3] Dr. Aringer explained, "Overall, it looks like belimumab works in most domains. Hematologic manifestations of SLE are the one big exception, and that's something we see in quite a few SLE drugs."[4]

"I think the most impressive part of belimumab is that it decreases the risk of severe flares when added to hydroxychloroquine," he continued. "It also increases the probability of remission, but both take some time."[5]

Dr. Aringer also expressed enthusiasm for anifrolumab, which may be a faster acting drug than belimumab. "We start to see a difference starting at four to eight weeks. We see the biggest impact on the mucocutaneous and musculoskeletal manifestations, and glucocorticoid dose reduction," he said.[6,7] Anifrolumab is also under investigation for the treatment of lupus nephritis, with phase 3 trials underway.[8]

In terms of safety, Dr. Aringer noted, "There's a statistically significant difference in herpes zoster infections, and a bit of a numerical signal for influenza. That makes sense since nature made interferon for fighting viral infections."[9]

Dr. Aringer mentioned voclosporin only briefly, as it's not yet widely available in Europe. He noted, however, that it has a "great and probably direct effect on proteinuria."[10]

Although never FDA approved, rituximab still has a role for certain people with SLE (e.g., cytopenias, neuropsychiatric SLE, lupus nephritis). "The randomized, controlled trials were negative, but there were real issues regarding trial duration, amount of glucocorticoids, etc. There are numerous large cohort publications in which we saw a lot of improvement across the field," Dr. Aringer said.[11,12] Rituximab is out-of-patent, thus new trials in SLE are unlikely. However, new anti-CD20 therapies, like obinutuzumab, are under further study in lupus nephritis.[13]

Baricitinib drug development in SLE was halted in January 2022 after two phase 3 studies failed to show adequate benefit.[14] However, case reports have noted impressive results for mucocutaneous manifestations of SLE.[15] "We'll learn more about the potential efficacy of Janus kinase inhibitors in SLE in the next few years. More trials are ongoing," Dr. Aringer said.

Although most rheumatologists avoid tumor necrosis factor-α (TNFα) inhibitors in SLE due to their association with drug-induced SLE, Dr. Aringer reminded us that an observational study demonstrated the safety and efficacy of etanercept for lupus arthritis.[16] "In really severe and untreatable lupus arthritis, one should be aware of this option," he said. These data are specific to etanercept, but not other TNFα inhibitors.

Tocilizumab may also be an option for severe lupus arthritis.[17] "Both the

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tocilizumab and etanercept trials were uncontrolled studies, but something to keep in your back pocket," he remarked.

Final Thoughts

SLE patients have heterogeneous manifestations of disease, and our SLE toolbox is beginning to match that diversity. When selecting a therapy, Dr. Aringer reminded us that not all SLE symptoms represent active autoimmunity, and therapies often need months to work.

"Take the individual SLE organ spectrum into account when choosing a drug. Be aware of the risks and uncertainties of off-label therapy, while bearing in mind that these patients need help, and there isn't a lot that's formally approved just yet," he concluded. 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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JAK Inhibitors *continued from page 47*

increased risk of cardiovascular outcomes, although not statistically significant, in patients with RA with cardiovascular risk factors. "There appears to only be a difference in risk in the 'at-risk' group, just like ORAL," he said.

Data from ORAL induced medical warnings for different JAK inhibitors across the world.[15,16] So are they safe and should we prescribe them for our patients or not? "Because of safety concerns, only use a JAK inhibitor if you explicitly consider the potential side effects for every patient," said Dr. Schulze-Koops. "In at-risk populations, I think we should wait until we have conclusive evidence as to why these increased risks happen before we close the book."

Promise 4: Simple Mechanism of Action

On a biochemical level, what do JAK inhibitors do? A kinase is an enzyme that transfers a phosphate residue to a substrate, and JAK inhibitors prevent this from occurring. However, the human body has 518 protein kinases. "In essence, the mechanism of action of JAK inhibitors is simple," said Dr. Schulze-Koops. "But if we try to inhibit just one kinase, we must accept that this will never be 100% selective or specific in any given life situation. We need to learn more to understand how exactly JAK inhibitors work, and how they put particular patient populations at particular risk."

In Sum

Dr. Schulze-Koops concluded his talk on a positive note. "Overall, I think that JAK inhibitors are wonderful and a perfect addition to our treatment armamentarium. However, there may be something [about JAK inhibitors] that's as dark as this room is without the lights on, and I'm looking forward to seeing that data. Only then will we be able to determine if all JAK inhibitor promises have been fulfilled." R

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MS. JOHNSON

Navigating the Employment Offer

Setting up a framework for success

■ BY EMILY A. JOHNSON, JD

There's nothing quite as exciting as answering a phone call to hear the words: "You're hired." After hours of research and preparation, multiple interviews and a healthy dose of daydreaming about your first day, you've made it across the finish line. Except for one final hurdle—the negotiation process. Don't overlook it. The negotiation process is a key determinant of success for a newly hired employee, and it doesn't have to be stressful.

Approaching Negotiations

The purpose: Many people who don't regularly engage in formal negotiations think the process is adversarial, combative and stressful. However, the main purpose of negotiations is not to create a winner and a loser, but to create a framework in which everyone involved is headed toward success.

The most important first step is to gather all of the information you're going to need. To get you started, here's a list of information and documents to have on hand in addition to your offer letter:

1. Public information about your employer (e.g., website, newspaper, word of mouth, court filings). Hopefully, you have a lot of this from your pre-interview research;
2. All information relevant to this position (e.g., job description, employment contract, benefit information, liability insurance coverage). If the employer has some of this information, ask for it;
3. The contact information of the person authorized to conduct the negotiation;
4. A timeline for the negotiation process. Confirm this timeline with the contact you've identified; and
5. Legal counsel. Issues can be lurking in unlikely places during a negotiation process. Competent legal counsel can help find them and craft creative solutions.

Finally, take a minute to gather your thoughts on what is important to you, personally and professionally. This will help guide you through negotiations, and match your goals and values with those of the employer.

Negotiation Issues

Some of the issues that may arise include:

Other duties as assigned: This phrase is ubiquitous in job descriptions and employment contracts. Often, the other duty is a simple request that is not quite what you do. But in the medical field, this can mean quite a bit more. Be sure to match this term up with your listed job duties and coverage requirements in the contract. Are there on-call obligations? Can you be told to move to a different shift without notice? If you think this may be a risk you're not willing to take, you might ask legal counsel to negotiate a provision in which you would be able to renegotiate your compensation if such an event occurs.

Compensation: It's important to consider all forms of compensation, and physicians and others working in healthcare should closely examine their compensation arrangement for potential legal problems. Two major concerns in a compensation arrangement are violations of the Stark law (i.e., physician self-referral) and the Anti-Kickback Statute. Broadly speaking, these laws protect Medicare and Medicaid from being billed as part of an inappropriate compensation arrangement. These arrangements can be complex and often seem innocent to the untrained eye. This is where legal counsel experienced in healthcare comes in. Unfortunately, a compensation structure that violates these laws cannot be negotiated. If an arrangement is improper, it must be restructured before anything is signed.

Professional liability insurance: Medical professionals should all have professional liability insurance to cover malpractice claims. In addition to knowing what plan your new employer is offering you, it is also important to know what sort of coverage you had in your previous position.

Determine if you have *occurrence-based* or *claims-based* coverage. Occurrence-based coverage plans are tied to alleged instances of malpractice. Claims-based coverage plans are tied to when the claim of malpractice is made. If you have occurrence-based coverage, you will be covered for any alleged instances of malpractice that occurred while you were under that plan. If you have claims-based coverage, you may need a *tail coverage* plan as well. Unless you stay with the same insurance company when you switch practices, your claims-based coverage will not cover any claims that originated during your time at the previous practice. Tail coverage can bridge that gap.

Before accepting your new job, make sure you know what coverage you will need to prevent headaches down the road. A point of negotiation may be whether you or your employer will pay for the tail coverage. After all, your new employer certainly would rather have you working than distracted by a costly malpractice claim.

Outside work: It's important to know how much control your employer has over your work for organizations other than the employer. Contracts may have a provision that prevents you from providing medical services for anyone but your employer. This could prevent moonlighting, speaking or even volunteering. Employers may have a legitimate reason to prevent you from doing these things. However, if it's important that you be able to engage in your profession outside this employment contract, it may be time to head to the negotiation table.

If you have a specific request, your employer may grant it. Or the employer may allow you to participate in certain activities under the condition that you remit all earnings from those activities to the employer. This may seem unfair, but could give you leverage in future discussions about compensation increases.

Restrictive covenants: Restrictive covenants, also known as *non-competes,* are common. Generally, a restrictive covenant limits what an employee can do after they leave their current job. For example, a physician who leaves a practice may have a restrictive covenant that prevents them from practicing medicine within a 50-mile radius of the current practice for two years after they leave their current job. A restrictive covenant may also prevent a physician from recruiting employees or patients away from the current practice.

Whether, and to what extent, a restrictive covenant will be enforced varies from state to state. Regardless, it's important to review your contract for what you may not be able to do after your employment ends. Try to imagine how difficult it would be to make a living if you left this position. If you think it could affect your life or career path, it may be time to negotiate a reduced restriction, such as a smaller non-compete radius or a shorter lifespan of the covenant. A lawyer can help determine how your state will enforce a non-compete, which will create leverage during negotiations for a less restrictive covenant.

Employee vs. independent contractor: Another important consideration when reviewing your employment contract is whether you will be considered an employee or an independent contractor. A section in the contract will explicitly describe your relationship to the employer. From tax obligations to having control over your work to stability of work, your employment status determines a lot. Review the description of the arrangement from a practical standpoint to determine if any deal-breakers are present.

Your employment status can also have major implications when determining whether your contract complies with the Stark law and the Anti-Kickback Statute. As discussed above, an experienced healthcare attorney can help ensure you are not running afoul of any major laws.

Sign on the Dotted Line

By approaching employment negotiations as a collaboration, you demonstrate to your employer that you are considerate, focused and grounded. Reach out to an attorney experienced with reviewing employment agreements well in advance of your anticipated start date to ensure the process is completed timely and effectively. R

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Movers & Shakers

Awards, appointments & announcements in the world of rheumatology

■ BY GRETCHEN HENKEL

Roberto Caricchio, MD, Now Chief of Rheumatology at UMass Chan Medical School

As of July 1, **Roberto Caricchio, MD**, began a new appointment as chief of the Division of Rheumatology at UMass Chan Medical School, Worcester. He was formerly chief of the Section of Rheumatology at Lewis Katz School of Medicine at Temple University, Philadelphia, where he was also a professor of medicine, microbiology and immunology, as well as director of the Temple Lupus Program. Dr. Caricchio has also been named the Myles J. McDonough Chair in Rheumatology, a position formerly held by past ACR President Ellen M. Gravallese, MD, who is now chief of the Division of Rheumatology, Inflammation and Immunity at Brigham and Women's Hospital, Boston.

We spoke with Dr. Caricchio during the transitional period between his acceptance of the new assignment and his move to Worcester. Dr. Caricchio's major interest in lupus will remain, but he is also going to have the opportunity to foster the growth of other physician-scientists, "a part of my career that is dear to me."

With palpable excitement, he explained that moving to UMass meant joining a medical institution entrenched in research. He will be among numerous physician-scientists—including David D. McManus, MD, chair of medicine and a leading authority in cardiovascular digital health, and Terence R. Flotte, MD, the provost, dean and executive deputy chancellor, who is an internationally known scientist in molecular therapeutics. The proximity of so many other physician-scientists will foster "the type of discussions and interactions that are what a physician-scientist needs," says Dr. Caricchio.

Clinical opportunities will also abound. His vision includes developing streamlined mechanisms to decrease wait times for patients with severe disease, growing a strong lupus program, offering patients the opportunity to join clinical trials and expanding translational research. Building the multidisciplinary clinics will also be part of the mix, he says, because it has been established that rheumatology patients who have joint access to other disciplines, such as nephrology, pulmonology and dermatology, experience better quality of care.

Dr. Caricchio will be passing the baton for work on a major study conducted while he was a core member of Temple University Hospital's COVID-19 Response Team. He spearheaded the development of a new strategic therapeutic approach to treating patients with coronavirus inflammatory response and predictors of poor outcome.[1] Of that effort, Dr. Caricchio says it was both "professionally and scientifically spectacular, but from a human point of view, seeing so many individuals succumb to a disease at one time … was terrible."

Dr. Caricchio obtained his medical degree from the Catholic University of Sacred Heart in Rome, and moved to the U.S. in 1996 to pursue a research fellowship at the University of North Carolina at Chapel Hill. A research faculty appointment at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, and a residency and additional fellowship at Temple University followed.

His wife and collaborator, immunologist Stefania Gallucci, MD, joins him at UMass, with an appointment as professor in the Division of Innate Immunity, directed by Katherine A. Fitzgerald, PhD.

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N.J. Rheumatologist Rita Komboz, MD, Adds Fiction Authorship to Her Credits

Rita Fares Komboz, MD, FACR, who has been in private practice as a rheumatologist in Belleville, N.J., for 23 years, found that she had a little more time on her hands when the COVID-19 pandemic necessitated the nationwide shutdown in spring 2020. She began a personal project that developed into the publication of a fanciful children's book, *Corky the Cat*.

Dr. Komboz drew her inspiration about the book's character from her own rescue cat. She made Corky a fashion designer. The book's narrative follows the plucky cat from her rise as a fashion designer at *Vogue*, through a coronavirus-caused career derailment and ultimate triumph over difficult circumstances. To accompany the text, Dr. Komboz composed color-saturated illustrations on her iPhone 7. She had originally thought to self-publish, but instead contacted Page Publishing, which printed the book in the U.S. The book is now available through Amazon, Barnes & Noble and other bookstores.

Coming of age in Lebanon during that country's civil war, Dr. Komboz recalls that she was drawn to medicine because she "wanted to make a difference." She obtained her medical degree from Université Saint-Joseph Faculté de Médecine, Beirut, in 1991.

She and her husband, a cardiologist, later emigrated to the U.S., where she finished an internship in Newark, N.J., and then a rheumatology fellowship in Philadelphia in 1999 at Allegheny Health Network. She recalls her fellowship coincided with the release of TNF inhibitors, such as etanercept, which was a game-changer in the treatment armamentarium for patients with rheumatoid arthritis.

Dr. Komboz is a rheumatologist with Arthritis and Osteoporosis Associates, Belleville, N.J., and is also affiliated with Clara Maass Medical Center, also in Belleville.

She has plans for a *Corky the Cat* sequel, and the protagonist may find herself a rheumatologist in her second life.

Richard S. Panush, MD, Recipient of 2022 AAIM-APDIM Distinguished Medical Educator Award

During Academic Internal Medicine Week 2022, sponsored by the Alliance for Academic Internal Medicine (AAIM), April 10–13, **Richard S. Panush, MD, MACP, MACR,** received the Distinguished Medical Educator Award from the Association of Program Directors in Internal Medicine. Dr. Panush is a professor of medicine emeritus, Division of Rheumatology, Keck School of Medicine at the University of Southern California, Los Angeles.

As early as his third year of medical school at the University of Michigan, Ann Arbor, Dr. Panush found that rheumatology "posed some of the most interesting and challenging clinical and investigative questions in medicine." His influences included the late Giles Bole, MD, a former dean of the medical school and past president of the ACR; the late C. William Castor, MD; the late James B. Wyngaarden, MD, who was the residency chair at Duke University, Durham, N.C., during Dr. Panush's time there, and subsequently director of the National Institutes of Health (NIH); and William N. Kelley, MD, MACP, "when he had just come to Duke as this a bright young rheumatologist from the NIH." Dr. Kelley is another ACR past president and current professor of medicine at the University of Pennsylvania.

Dr. Panush cites other important influences from his rheumatology fellowship at the Robert Breck and Peter Bent Brigham Hospitals (now known as the Brigham and Women's Hospital, Boston): Peter H. Schur, MD, professor of medicine, Brigham and Women's Hospital, and K. Frank Austen, MD, the AstraZeneca Professor of Respiratory and Inflammatory Diseases at Harvard Medical School.

Dr. Panush's multi-faceted career has included academic appointments at the University of Florida College of Medicine, Gainesville; Saint Barnabas Medical Center, Livingston, N.J.; University of Medicine and Dentistry, New Jersey Medical School, Newark; and Mount Sinai School of Medicine, N.Y.

Throughout his career Dr. Panush has maintained a passionate interest in the interface of medicine with the humanities; he has studied and written extensively about this. As the chair of the ACR's Ethics Committee, Dr. Panush played a critical role in helping identify Nazi physicians who had been recognized with eponymic honors and having their names removed from the diseases with which they had been associated. They should be remembered "in obloquy and shame for their violation of transcendent ethical and moral responsibilities," he says.

Dr. Panush was a residency or fellowship program director for 40 of his 50 years in academic medicine, and division chief or department chair for 35. "At some point in your career, you realize it's not about you," he says. "It's about the program you're in, and the organization and community you represent. What's important is how you influence others, how you support them in their careers and how you try to make people, programs, rheumatology and our world better."

Of his recent recognition by the AAIM, he says that "at this time in my life and career, this is a humbling honor indeed." R

Gretchen Henkel is a health and medical journalist based in California.

Reference

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Biologic or Conventional Therapy for Early RA?

Plus baricitinib promising for JIA

■ BY MICHELE B. KAUFMAN, PHARMD, BCGP

EULAR 2022 (VIRTUAL)

Therapy for Early RA

Østergaard et al. compared the radiographic and clinical outcomes of active conventional therapy for patients with rheumatoid arthritis (RA) with the outcomes of patients with RA treated with three biologic therapies with different mechanisms of action. Mikkel Østergaard, MD, Rigshospitalet, Center for Rheumatology and Spine Diseases, Glostrup, Denmark, presented the results of this open-label, blind-assessor study during the 2022 Congress of the European Alliance of Associations for Rheumatology (EULAR).[1]

To be enrolled in the study (NCT01491815), adult patients had to have treatment-naive early RA with a symptom duration of less than 24 months and a Disease Activity Score-28 (DAS-28) for RA with C-reactive protein (CRP) of >3.2. Patients also had to have a minimum of two swollen and tender joints, as well as at least one of the following: positivity for rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), and/or a CRP level of >10 mg/L.[2]

The researchers randomized 812 patients, mostly women, with a mean age of 55 years in a 1:1:1:1 ratio to receive 25 mg of methotrexate weekly combined with one of four treatment regimens: 1) 20 mg of oral prednisolone daily tapered over nine weeks to 5 mg daily, then discontinued at week 36; or 2 g of sulfasalazine daily; or 35 mg/kg of hydroxychloroquine weekly; and mandatory intra-articular glucocorticoid injections in swollen joints (active conventional therapy); 2) 200 mg of subcutaneous certolizumab pegol administered every other week; 3) 125 mg of subcutaneous abatacept administered every week; or 4) tocilizumab administered as four weekly infusions of 8 mg/kg of bodyweight or 162 mg given as a subcutaneous solution weekly.

The primary study outcomes at week 48 were the proportion of patients in remission according to the Clinical Disease Activity Index (CDAI ≤2.8) and a change in the radiographic progression in the total van der Heijde-modified Sharp Score from baseline. The primary end points were estimated using logistic regression and analysis of covariance, adjusted for sex, ACPA status and the country where patients live.

Results: The adjusted CDAI remission rates at week 48 for each group were 59.3% for abatacept; 52.3% for certolizumab pegol; 51.9% for tocilizumab; and 39.2% for active conventional therapy. Because two primary outcomes were examined, significance was defined as a *P* value ≤0.25. For the CDAI remission rates of the biologic agents, abatacept ($P<0.001$) and certolizumab pegol ($P=0.021$) were superior to active conventional therapy. For CDAI remission rates, the difference in remission rates for tocilizumab did not achieve formal statistical significance ($P=0.030$). The adjusted mean change in the total modified Sharp-van der Heijde score from baseline was low, indicating no significant differences between the four treatments related to radiographic progression.

Key secondary clinical outcomes were consistently better in the biologic treatment groups. These outcomes included: CDAI remission at week 24, DAS-28 remission at weeks 12 and 24, and EULAR Good Response. Key secondary outcomes demonstrated no major differences among the four treatments.

Serious adverse events, which were not delineated in the abstract, occurred in each treatment group: 28 in the certolizumab pegol group, 23 in the active conventional therapy group, 32 in the abatacept group and 20 in the tocilizumab group. No new safety signals were reported during the study.

This study showed that in untreated patients with early RA, CDAI remission rates for abatacept and certolizumab pegol were superior to active conventional treatment. Radiographic progression was low and similar among all treatments evaluated.

Baricitinib for JIA

Another study presented at EULAR found oral baricitinib (Olumiant) significantly reduced the time to, and frequency of, flares in patients aged 2–18 years with juvenile idiopathic arthritis (JIA).[3] The findings of the study were presented by Athimalaipet Ramanan, MD, FRCPCH, FRCP, a consultant pediatric rheumatologist at Bristol Royal Hospital for Children and Royal National Hospital for Rheumatic Diseases, Bath, U.K., and Bristol Royal Hospital for Children, Bristol Medical School, Bristol, U.K.

Baricitinib is a Janus kinase (JAK) 1/2 selective inhibitor. In May 2018, the U.S. Food & Drug Administration (FDA) approved the agent to treat adults with moderate to severe active RA for whom one or more tumor necrosis factor (TNF) antagonist therapies had proved inadequate.[4] In a phase 3 study, Ramanan et al. investigated baricitinib's safety and efficacy in pediatric patients with JIA for whom conventional or biologic disease-modifying anti-rheumatic drugs (DMARDs) had proved inadequate.

Participants in this double-blind, withdrawal study included patients with extended oligoarticular or polyarticular JIA, enthesitis-related arthritis (ERA) or juvenile psoriatic arthritis (jPsA) according to the International League of Associations for Rheumatology (ILAR) criteria.

Study design: The study was divided into three periods: a two-week pharmacokinetic and safety assessment; a 12-week, open-label, lead-in period; and a 32-week, double-blind withdrawal period. Safety and dosing were confirmed during the pharmacokinetic and safety assessment period. Patients enrolled in the open-label, lead-in period then received age-based, once-daily doses of baricitinib. Patients who achieved a JIA ACR30 response at week 12 entered the study's double-blind withdrawal phase. In the double-blind withdrawal period, patients were randomized in a 1:1 ratio to continue baricitinib treatment or begin baricitinib withdrawal, receiving placebo until disease flare or week 32.

The primary study end point was the time to flare during the double-blind withdrawal period. Secondary end points included the proportion of patients experiencing a flare during the double-blind withdrawal period and the JIA ACR30/50/70/90 response rates at week 12. Survival curves were estimated using the Kaplan-Meier method.

The results: In total, 219 patients entered the study's second phase—the 12-week, open-label, lead-in period—and 163 patients entered the 32-week, double-blind withdrawal period.

At week 12, 76.3% of patients achieved a JIA ACR30 response, 63.5% of patients achieved a JIA ACR50 response, 46.1% of patients achieved a JIA ACR70 response and 20.1% of patients achieved a JIA ACR90 response. During the double-blind withdrawal period, the proportion of patients who experienced a disease flare was significantly lower in the baricitinib treatment group (17.1%) than the placebo group (50.6%; $P<0.001$).

In the pharmacokinetic and safety assessment and open-label, lead-in parts of the study, 126 patients (57.3%) reported treatment-emergent adverse events, and six patients (2.7%) reported at least one serious adverse event. The most common treatment-emergent adverse events in both groups were nasopharyngitis (n=19; 8.6%), headache (n=14; 6.4%), arthralgias (n=12; 5.5%), upper respiratory tract infection (n=11; 5%) and nausea (n=11; 5%). Serious adverse events included arthralgias (n=1; 0.5%), joint destruction (n=1; 0.5%), joint effusion (n=1; 0.5%), JIA (n=1; 0.5%), musculoskeletal chest pain (n=1; 0.5%) and decreased appetite (n=1; 0.5%). One case of herpes virus (0.5%) and one case of herpes zoster (0.5%) were also reported.

In the study's double-blind withdrawal period, at least one treatment-emergent adverse event was reported for patients who received placebo (n=38; 46.9%) and for patients treated with baricitinib (n=54; 65.9%). Three (3.7%) and four (4.9%) serious adverse events occurred in patients who received placebo and baricitinib, respectively. Due to the study design, the mean number of weeks of exposure was higher in the baricitinib group (26.3 weeks) compared with the placebo group (18.9 weeks) during this study period.

No deaths, cardiovascular events or uveitis were reported, and no new safety signals were identified during the study.

In this study, baricitinib significantly reduced time to JIA flare and frequency of JIA flares in young patients, with improved JIA ACR response scores in most patients within 12 weeks. The safety findings were consistent with the known safety profile of baricitinib in adults with RA.

These results support the use of baricitinib to treat patients aged 2–18 years with signs and symptoms of JIA for whom conventional or biologic DMARDs have proved inadequate. **R**

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References

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2. Active conventional therapy compared to three different biologic treatments in early rheumatoid arthritis with subsequent dose reduction [NCT01491815]. ClinicalTrials.gov. 2021 Jul 27.
3. Ramanan A, Quartier P, Okamoto N, et al. Baricitinib in juvenile idiopathic arthritis: A phase 3, double-blind, placebo-controlled, withdrawal, efficacy and safety study [LB0002]. *Ann Rheum Dis*. 2022:81(suppl 1): 207–208.
4. New drug application approval letter: Olumiant (baricitinib). U.S. Food & Drug Administration. 2018 May 31.

TAVNEOS® (AVACOPAN) CAPSULES FOR ORAL USE BRIEF SUMMARY OF THE FULL PRESCRIBING INFORMATION (PI) — RX ONLY

INDICATIONS AND USAGE

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

DOSAGE AND ADMINISTRATION

Recommended Evaluations Prior to Treatment Initiation

Before initiating TAVNEOS, consider performing the following evaluations:

- Liver Function Tests: Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS. TAVNEOS is not recommended for use in patients with cirrhosis, especially those with severe hepatic impairment (Child-Pugh C) *[see Warnings and Precautions (Full PI 5.1) and Use in Specific Populations (Full PI 8.7)]*.
- Hepatitis B (HBV) Serology: Screen patients for HBV infection by measuring HBsAg and anti-HBc. For patients with evidence of prior or current HBV infection, consult with a physician with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before or during treatment with TAVNEOS *[see Warnings and Precautions (Full PI 5.3)]*.

Recommended Dosage and Administration

The recommended dose of TAVNEOS is 30 mg (three 10 mg capsules) twice daily, with food.

Advise patients that TAVNEOS capsules should not be crushed, chewed or opened.

If a dose is missed, instruct the patient to wait until the usual scheduled time to take the next regular dose. Instruct the patient not to double the next dose.

Dosage Modifications Due to CYP3A4 Inhibitors

Reduce the dosage of TAVNEOS to 30 mg once daily when used concomitantly with strong CYP3A4 inhibitors.

CONTRAINDICATIONS

TAVNEOS is contraindicated in patients with serious hypersensitivity reactions to avacopan or to any of the excipients *[see Warnings and Precautions (Full PI 5.2)]*.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking TAVNEOS. During controlled trials, the TAVNEOS treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events *[see Adverse Reactions (Full PI 6.1)].*

Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS, every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.

If a patient receiving treatment with TAVNEOS presents with an elevation in ALT or AST to >3 times the upper limit of normal, evaluate promptly and consider pausing treatment as clinically indicated.

If AST or ALT is >5 times the upper limit of normal, or if a patient develops transaminases >3 times the upper limit of normal with elevation of bilirubin to >2 times the upper limit of normal, discontinue TAVNEOS until TAVNEOS-induced liver injury is ruled out *[see Adverse Reactions (Full PI 6.1)]*.

TAVNEOS is not recommended for patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risk and benefit before administering this drug to a patient with liver disease. Monitor patients closely for hepatic adverse reactions *[see Use in Specific Populations (Full PI 8.7)]*.

Hypersensitivity Reactions

TAVNEOS may cause angioedema *[see Adverse Reactions (Full PI 6.1)]*. In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization. If angioedema occurs, discontinue TAVNEOS immediately, provide appropriate therapy, and monitor for airway compromise. TAVNEOS must not be re-administered unless another cause has been established. Educate patients on recognizing the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program.

HBV reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg, in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Screen patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TAVNEOS. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TAVNEOS treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis, or HBV reactivation during and for six months following TAVNEOS therapy. In patients who develop reactivation of HBV while on TAVNEOS, immediately discontinue TAVNEOS and any concomitant therapy associated with HBV reactivation, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming TAVNEOS treatment in patients who develop HBV reactivation. Resumption of TAVNEOS treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Serious Infections

Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections.

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

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection

- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with TAVNEOS. Interrupt TAVNEOS if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with TAVNEOS should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and TAVNEOS should be interrupted if the patient is not responding to antimicrobial therapy. TAVNEOS may be resumed once the infection is controlled.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Hepatotoxicity *[see Warnings and Precautions (Full PI 5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (Full PI 5.2)]*
- Hepatitis B Virus (HBV) Reactivation *[see Warnings and Precautions (Full PI 5.3)]*
- Serious Infections *[see Warnings and Precautions (Full PI 5.4)]*

Clinical Trials Experience

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

The identification of potential adverse drug reactions was based on safety data from the phase 3 clinical trial in which 330 patients with ANCA-associated vasculitis were randomized 1:1 to either TAVNEOS or prednisone *[see Clinical Studies (Full PI 14)]*. The mean age of patients was 60.9 years (range of 13 to 88 years), with a predominance of men (56.4%) and Caucasians (84.2%). The cumulative exposure to TAVNEOS was 138.7 patient-years. Additionally, two phase 2 trials were conducted in ANCA-associated vasculitis. The cumulative clinical trial exposure from the phase 2 and 3 trials equals 212.3 patient-years.

The most frequent serious adverse reactions reported more frequently in patients treated with TAVNEOS than with prednisone were pneumonia (4.8% TAVNEOS vs. 3.7% prednisone), GPA (3.0% TAVNEOS vs. 0.6% prednisone), acute kidney injury (1.8% TAVNEOS vs. 0.6% prednisone), and urinary tract infection (1.8% TAVNEOS vs. 1.2% prednisone). Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and 2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the phase 2 trials.

In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzymes abnormalities. The most frequent adverse reaction that led to drug discontinuation reported by > 1 patient and more frequently reported in patients treated with TAVNEOS was hepatic function abnormal (1.8%).

The most common adverse reactions that occurred in ≥5% of patients and higher in the TAVNEOS group as compared with the prednisone group are listed in Table 1.

Table 1: Adverse Reactions Reported in ≥5% of Patients and Higher in TAVNEOS Group vs. Prednisone Group in Phase 3 Trial

Adverse Reaction	Prednisone (N=164) n (%)	TAVNEOS (N=166) n (%)
Nausea	34 (20.7)	39 (23.5)
Headache	23 (14.0)	34 (20.5)
Hypertension	29 (17.7)	30 (18.1)
Diarrhea	24 (14.6)	25 (15.1)
Vomiting	21 (12.8)	25 (15.1)
Rash	13 (7.9)	19 (11.4)
Fatigue	15 (9.1)	17 (10.2)
Upper abdominal pain	10 (6.1)	11 (6.6)
Dizziness	10 (6.1)	11 (6.6)
Blood creatinine increased	8 (4.9)	10 (6.0)
Paresthesia	7 (4.3)	9 (5.4)

N=number of patients randomized to treatment group in the Safety Population; n=number of patients in specified category.

Hepatotoxicity and Elevated Liver Function Tests

In the phase 3 trial, a total of 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the TAVNEOS group had hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. Study medication was paused or discontinued permanently due to hepatic-related adverse reactions in 5 patients (3.0%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. Serious hepatic-related adverse reactions were reported in 6 patients (3.7%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. A serious hepatic-related adverse reaction was reported in 1 patient in the TAVNEOS group in the phase 2 studies.

Angioedema

In the phase 3 trial, 2 patients (1.2%) in the TAVNEOS group had angioedema; one event was a serious adverse reaction requiring hospitalization.

Elevated Creatine Phosphokinase

In the phase 3 trial, 1 patient (0.6%) in the prednisone group and 6 patients (3.6%) in the TAVNEOS group had increased creatine phosphokinase. One TAVNEOS-treated patient discontinued treatment due to increased creatine phosphokinase.

DRUG INTERACTIONS

CYP3A4 Inducers

Avacopan exposure is decreased when co-administered with strong CYP3A4 enzyme inducers such as rifampin *[see Clinical Pharmacology (Full PI 12.3)]*. Avoid coadministration of strong and moderate CYP3A4 inducers with TAVNEOS.

CYP3A4 Inhibitors

Avacopan exposure is increased when co-administered with strong CYP3A4 enzyme inhibitors such as itraconazole *[see Clinical Pharmacology (Full PI 12.3)]*. Administer TAVNEOS 30 mg once daily when coadministered with strong CYP3A4 inhibitors.

CYP3A4 Substrates

Avacopan is a CYP3A4 inhibitor. Closely monitor patients for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with a narrow therapeutic window when coadministered with TAVNEOS *[see Clinical Pharmacology (Full PI 12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with TAVNEOS in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of avacopan to pregnant hamsters and rabbits during the period of organogenesis produced no evidence of fetal harm with exposures up to approximately 5 and 0.6 times, respectively, the exposure at the maximum recommended human dose (MRHD) of 30 mg twice daily (on an area under the curve [AUC] basis). Avacopan caused an increase in the number of abortions in rabbits at an exposure 0.6 times the MRHD *(see Animal Data)*. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study with pregnant hamsters dosed by the oral route during the period of organogenesis from gestation days 6 to 12, avacopan produced an increase in the incidence of a skeletal variation, described as supernumerary ribs, at an exposure that was 5 times the MRHD (on an AUC basis with a maternal oral dose of 1000 mg/kg/day). No structural abnormalities were noted with exposures up to 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

In an embryo-fetal development study with pregnant rabbits dosed by the oral route during the period of organogenesis from gestation days 6 to 18, avacopan caused an increase in the number of abortions at an exposure 0.6 times the MRHD (on an AUC basis with a maternal oral dose of 200 mg/kg/day), however, no evidence of fetal harm was observed with such exposures. Maternal toxicity, as evidenced by decreased body weight gains, was observed at exposures 0.6 times and higher than the MRHD (on an AUC basis with maternal oral doses of 30 mg/kg/day and higher).

In a prenatal and postnatal development study with pregnant hamsters dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, avacopan had no effects on the growth and development of offspring with exposures up to approximately 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

Lactation

Risk Summary

There are no available data on the effects of avacopan on the breastfed child or on milk production. It is unknown whether avacopan is secreted in human milk. Avacopan was detected in the plasma of undosed hamster pups nursing from drug-treated dams *(see Animal Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAVNEOS and any potential adverse effects on the breast-fed infant from TAVNEOS or from the underlying maternal condition.

Animal Data

Avacopan has not been measured in the milk of lactating animals; however, it was detected in the plasma of nursing offspring in a pre- and post-natal development study with hamsters at a pup to maternal plasma ratio of 0.37. This finding suggests that avacopan is secreted into the milk of lactating hamsters *[see Nonclinical Pharmacology (Full PI 13.1)]*.

Pediatric Use

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

Geriatric Use

Of the 86 geriatric patients who received TAVNEOS in the phase 3 randomized clinical trial for ANCA-associated vasculitis *[see Clinical Studies (Full PI 14)]*, 62 patients were between 65-74 years and 24 were 75 years or older. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

Patients With Renal Impairment

No dose adjustment is required for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (Full PI 12.3)]*. TAVNEOS has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

Patients With Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (as indicated by the Child-Pugh method) hepatic impairment *[see Clinical Pharmacology (Full PI 12.3)]*. TAVNEOS has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Based on Prescribing Information approved on 10/2021.

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TAVNEOS®
(avacopan)

RELEASE

THE GRASP OF ANCA-ASSOCIATED VASCULITIS.

TAVNEOS® (avacopan) is a first-in-class, adjunctive treatment proven to help patients achieve and sustain remission.[1-4]

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

Discover more about TAVNEOS by scanning the QR code or visiting **TAVNEOS.com/hcp**

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Serious hypersensitivity to avacopan or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Serious cases of hepatic injury have been observed in patients taking TAVNEOS, including life-threatening events. Obtain liver test panel before initiating TAVNEOS, every 4 weeks after start of therapy for 6 months and as clinically indicated thereafter. Monitor patients closely for hepatic adverse reactions, and consider pausing or discontinuing treatment as clinically indicated (refer to section 5.1 of the Prescribing Information). TAVNEOS is not recommended for patients with active, untreated, and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risks and benefits before administering this drug to a patient with liver disease.

Serious Hypersensitivity Reactions: Cases of angioedema occurred in a clinical trial, including 1 serious event requiring hospitalization. Discontinue immediately if angioedema occurs and manage accordingly. TAVNEOS must not be readministered unless another cause has been established.

Hepatitis B Virus (HBV) Reactivation: Hepatitis B reactivation, including life-threatening hepatitis B, was observed in the clinical program. Screen patients for HBV. For patients with evidence of prior infection, consult with physicians with expertise in HBV and monitor during TAVNEOS therapy and for 6 months following. If patients develop HBV reactivation, immediately discontinue TAVNEOS and concomitant therapies associated with HBV reactivation, and consult with experts before resuming.

Serious Infections: Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections. Avoid use of TAVNEOS in patients with active, serious infection, including localized infections. Consider the risks and benefits before initiating TAVNEOS in patients with chronic infection, at increased risk of infection, or who have been to places where certain infections are common.

ADVERSE REACTIONS

The most common adverse reactions (≥5% of patients and higher in the TAVNEOS group vs. prednisone group) were nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, and paresthesia.

DRUG INTERACTIONS

Avoid coadministration of TAVNEOS with strong and moderate CYP3A4 enzyme inducers. Reduce TAVNEOS dose when coadministered with strong CYP3A4 enzyme inhibitors to 30 mg once daily. Monitor for adverse reactions and consider dose reduction of certain sensitive CYP3A4 substrates.

TAVNEOS is available as a 10 mg capsule.

INDICATION

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

Please see the Brief Summary of the Full Prescribing Information for TAVNEOS on the previous pages.

To report a suspected adverse event, call 1-833-828-6367. You may report to the FDA directly by visiting www.fda.gov/medwatch or calling 1-800-332-1088.

References: 1. TAVNEOS® (avacopan) Prescribing Information. ChemoCentryx, Inc. **2.** Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384(7):599-609. doi:10.1056/NEJMoa2023386 **3.** Khan MM, Molony DA. In ANCA-associated vasculitis, avacopan was superior to prednisone taper for sustained remission. *Ann Intern Med*. 2021;174(7):JC79. doi:10.7326/ACPJ202107200-079 **4.** U.S. Food and Drug Administration. Novel drug approvals for 2021. Published November 2021. Accessed November 4, 2021. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021

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