A SUPPLEMENT TO Rheumatology News

Best of 2019

The RA Report

Top News Highlights

EULAR revises its RA management recommendations

BY MITCHEL L. ZOLER
EXPERT ANALYSIS FROM EULAR 2019 CONGRESS

MADRID – Pending 2019 revisions to the European League Against Rheumatism recommendations for managing rheumatoid arthritis may be most notable for two discussed changes that were tabled: no change to designating methotrexate the first disease-modifying drug to prescribe, before any biologic drug; and no adoption of imaging criteria to determine whether a patient is in remission.

"Imaging with ultrasound or MRI is out" as a remission criterion. "It's high risk and a waste of resources," declared Josef S. Smolen, MD, head of the EULAR writing panel, in the most forceful declaration he made while presenting the pending recommendation revision at the European Congress of Rheumatology.

Dr. Smolen's strong warning against an imaging parameter when treating RA patients toward a remission target was no surprise, as he had already voiced this opinion in an editorial he coauthored earlier this year (JAMA. 2019 Feb 5;321[5]:457-8). The editorial cited data from three independent studies that compared an RA treatment strategy that used an imaging measure of joint inflammation as a treatment target along with clinical assessment against clinical assessment alone. All three studies found no benefit from ultrasound or MRI for defining a treatment goal, and two of the studies showed evidence for harm. "Using imaging to guide therapy led to prescription of potentially harmful medicines without differences in the primary outcomes, but at high costs and potential burden of unnecessary treatment changes and risks for patients," noted Dr. Smolen and his coauthor in the editorial.


Mitchel L. Zoler/MDedge News

Dr. Josef S. Smolen: "Imaging with ultrasound or MRI is out" as a remission criterion. "It's high risk and a waste of resources."

The report that this editorial addressed (JAMA. 2019 Feb 5;321[5]:461-72) also provided some of the most recent evidence for the second omission from the new revision that Dr. Smolen called out: no change to the recommendation to use methotrexate as initial treatment for any RA patient. "We continue to say that methotrexate is the first treatment strategy. There is no new evidence that any biological treatment is better than methotrexate, so there is no change," said Dr. Smolen, professor of medicine at the Medical University of Vienna, who also led the EULAR writing panel for the immediately preceding set of RA treatment recommendations first unveiled 3 years before (Ann Rheum Dis. 2017 Jun;76[6]:960-77).

Perhaps the most notable changes to the recommendations are the way they handle targeted-synthetic disease-modifying antirheumatic drugs (tsDMARDs), a class that currently is synonymous with the Janus kinase (JAK) inhibitors. "Because of new evidence we have lifted up the tsDMARDs" so that no preference is given to biologic DMARDs over the ts class as happened in the 2016 version, Dr. Smolen said. Another revision to this recommendation was to change the addition of either a biologic or tsDMARD to a patient not fully responsive to a conventional-synthetic (cs) DMARD and with poor prognostic factors from a "should be considered" to a "should be added" recommendation.

Another way in which the pending revision uplifted tsDMARDs was in the wording for the recommendation

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Rheumatology News
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Best of 2019: The RA Report is a supplement to Rheumatology News, an independent newspaper that provides the practicing rheumatologist with timely and relevant news and commentary about clinical developments in the field and about the impact of health care policy on the specialty and the physician's practice.

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MDedge

For your adult patients with moderately to severely active RA who have had an inadequate response or intolerance to 1 or more DMARD(s)

When It's Time for a Change, Target IL-6R with KEVZARA

Learn more about controlling signs and symptoms of RA at **KEVZARAhcp.com**

KEVZARA helps inhibit the effects of chronically elevated IL-6[1]

IL-6R=interleukin-6 receptor.

KEVZARA®
(sarilumab) injection
200 mg | 150 mg

INDICATION

KEVZARA is indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with KEVZARA are at increased risk for developing serious infections that may lead to hospitalization or death. Opportunistic infections have also been reported in patients receiving KEVZARA. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Avoid use of KEVZARA in patients with an active infection.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before KEVZARA use and during therapy. Treatment for latent infection should be initiated prior to KEVZARA use.**
- **Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. If a serious infection develops, interrupt KEVZARA until the infection is controlled.

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including **Boxed WARNING,** on following pages.

WHEN IT'S TIME FOR A CHANGE, TARGET IL-6R WITH

KEVZARA® (sarilumab) injection

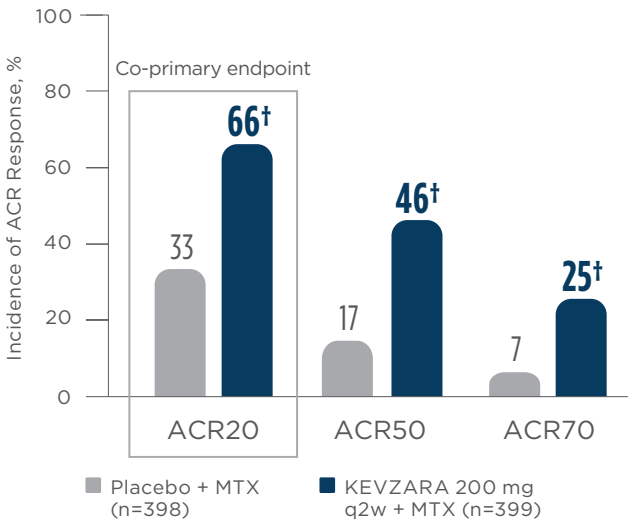
200 mg | 150 mg

SIGNIFICANT IMPROVEMENTS IN ACR CLINICAL RESPONSE AND PHYSICAL FUNCTION

KEVZARA combination therapy provided greater improvements in signs and symptoms of RA vs DMARD(s)

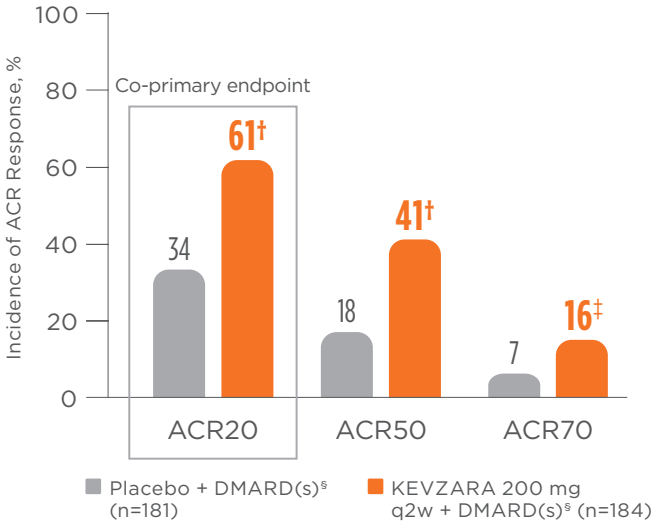
MOBILITY (MTX-IR)

ACR RESPONSES AT WEEK 24[1,2*]



TARGET (TNF-IR)

ACR RESPONSES AT WEEK 24[1,3*]



*After week 16 in MOBILITY and week 12 in TARGET, patients with an inadequate response could have been treated with open-label KEVZARA 200 mg every 2 weeks.
†$P<0.0001$; ‡$P<0.01$; §DMARD(s) in TARGET include MTX, sulfasalazine, leflunomide, and/or hydroxychloroquine.

ΔHAQ-DI AT WEEK 16 IN MOBILITY AND WEEK 12 IN TARGET (CO-PRIMARY ENDPOINT)[1-4]

- -0.58* with KEVZARA 200 mg + MTX vs -0.30 with placebo + MTX (MOBILITY)
- -0.49† with KEVZARA 200 mg + DMARD(s) vs -0.29 with placebo + DMARD(s) (TARGET)

*$P<0.0001$; †$P<0.001$.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATION

Do not use KEVZARA in patients with known hypersensitivity to sarilumab or any of the inactive ingredients.

WARNINGS AND PRECAUTIONS

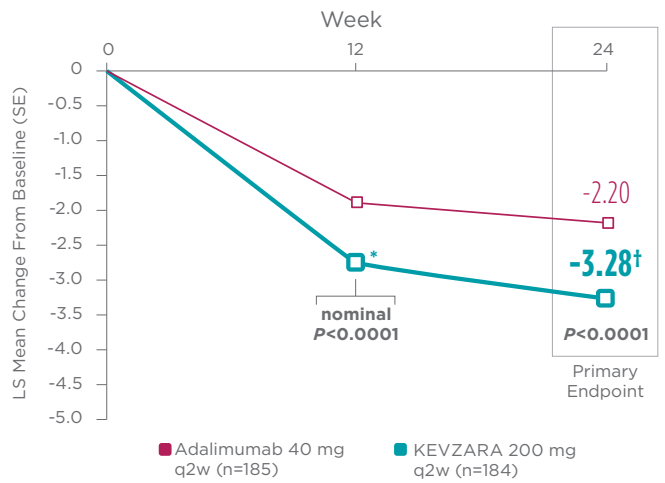
- ***Infections.*** Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents for rheumatoid arthritis (RA). The most frequently observed serious infections with KEVZARA included pneumonia and cellulitis. Among opportunistic infections, TB, candidiasis, and pneumocystis were reported with KEVZARA.
  - Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection.
  - Patients with latent TB should be treated with standard antimycobacterial therapy before initiating KEVZARA. Consider anti-TB therapy prior to initiation of KEVZARA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but having risk factors for TB infection.
  - Consider the risks and benefits of treatment prior to initiating KEVZARA in patients who have: chronic or recurrent infection, a history of serious or opportunistic infections, underlying conditions in addition to RA that may predispose them to infection, been exposed to TB, or lived in or traveled to areas of endemic TB or endemic mycoses.
  - Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with KEVZARA.

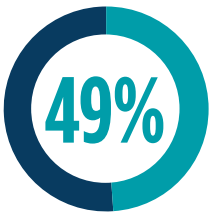
Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including **Boxed WARNING,** on following pages.

GREATER IMPROVEMENT IN DISEASE ACTIVITY vs ADALIMUMAB

KEVZARA monotherapy provided greater improvements in disease activity and signs and symptoms of RA for more patients vs adalimumab monotherapy (as measured by greater reductions in DAS28-ESR; primary endpoint)[5]

CHANGE IN DAS28-ESR AT WEEK 24





greater improvement in DAS28-ESR
than adalimumab at week 24[5]

*Difference: -1.08 (95% CI: -1.36 to -0.79).

AT WEEK 24

More than **3x** as many **KEVZARA patients achieved low disease activity (DAS28-ESR <2.6) vs adalimumab monotherapy**
(26.6% vs 7.0%; *P*<0.0001)[5]

The most common adverse events occurring in ≥3% of patients administered KEVZARA 200 mg and greater than observed in patients on adalimumab 40 mg: Infections (28.8% KEVZARA, 27.7% adalimumab); Neutropenia (13.6%, 0.5%); Headache (3.8%, 6.5%); Rheumatoid arthritis (0.5%, 3.8%); Injection site erythema (7.6%, 3.3%); Alanine aminotransferase increased (3.8%, 3.8%); Accidental overdose (3.3%, 6.0%); Dyslipidemia (1.6%, 4.3%); and at least 1 serious infection (1.1%, 1.1%).[5]

MONARCH Study Design: A 24-week, randomized, double-blind, double-dummy, phase 3 superiority study to evaluate the efficacy and safety of KEVZARA 200 mg q2w monotherapy (n=184) vs adalimumab 40 mg q2w monotherapy (n=185) in patients who should not continue treatment with MTX due to intolerance or inadequate response.†‡§ The primary endpoint was ΔDAS28-ESR; secondary endpoints included ΔDAS28-ESR <2.6, ACR20/50/70, ΔDAS28-CRP, ΔHAQ-DI.[5]

Additional Study Context

- MONARCH data are not included in the KEVZARA full Prescribing Information
- DAS28-ESR and FACIT-Fatigue were endpoints in MONARCH; however, there are no DAS28-ESR or FACIT-Fatigue data in the KEVZARA USPI

Use of Adalimumab

- Adalimumab and KEVZARA have different indications and can be used differently in clinical practice
- Dose escalation from adalimumab 40 mg q2w to qw was permitted after week 16 in patients who had not achieved at least 20% improvement in TJC and SJC. By week 24, dosing for 8.6% of patients on adalimumab was adjusted

Study Limitations

- KEVZARA and adalimumab can be used as monotherapy or in combination with nonbiologic DMARD(s). In MONARCH, both agents were only used as monotherapy
- The efficacy of KEVZARA monotherapy has not been compared to that of KEVZARA + MTX or adalimumab + MTX
- MONARCH did not evaluate radiographic outcomes in either treatment group

Given the limitations and context described above, caution should be used in interpreting these data.

†Efficacy analyses were conducted in the ITT population, which included all randomized patients, including those who increased the dose frequency of adalimumab or matching placebo. Data collected after permanent treatment discontinuation period were excluded.[5]
‡After week 16, dose escalation to adalimumab qw was permitted for patients who did not achieve ≥20% improvement in TJC and SJC.[5]
§The recommended dose of adalimumab SC is 40 mg q2w. Some patients not taking concomitant MTX may derive additional benefit from increasing the SC dosing frequency to 40 mg qw; see adalimumab full Prescribing Information.[6]

USPI=United States Prescribing Information; DAS28-ESR=disease activity score 28-erythrocyte sedimentation rate; TJC=tender joint count; SJC=swollen joint count; ITT=intent to treat.

WHEN IT'S TIME FOR A CHANGE, TARGET IL-6R WITH

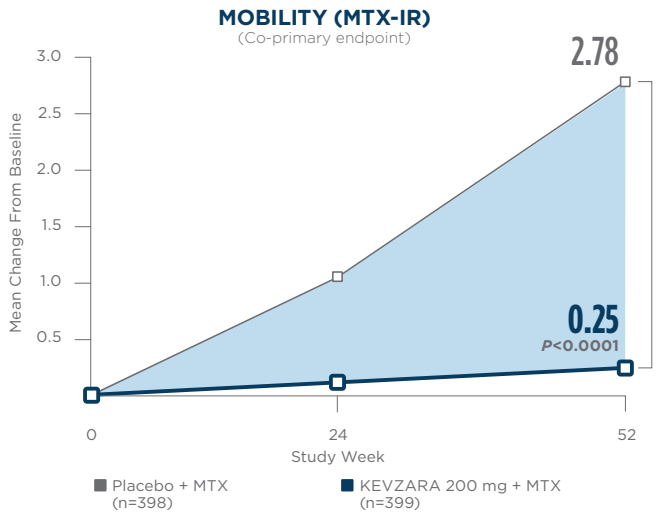
KEVZARA®
(sarilumab) injection
200 mg | 150 mg

56% OF MTX-IR PATIENTS HAD NO RADIOGRAPHIC PROGRESSION AT WEEK 52 WITH KEVZARA

vs 39% OF PATIENTS TREATED WITH PLACEBO[1]*

*Defined by change in mTSS ≤0.

MEAN CHANGE IN mTSS AT WEEK 52[1,2]



91%† **greater inhibition of joint damage progression** with KEVZARA 200 mg + MTX vs placebo + MTX

KEVZARA 200 mg + MTX provided an absolute difference of -2.52 units (CI: -3.38, -1.66) in mean ΔmTSS relative to placebo + MTX

†Based on post hoc comparisons of mean change in mTSS per treatment group. Week 52 analysis employs linear extrapolation method to impute missing or post-rescue data.

MOBILITY Study Design: A 52-week, randomized, double-blind placebo-controlled, multicenter study (N=1197) assessing the efficacy and safety of KEVZARA 200 mg + MTX and 150 mg + MTX in patients with moderate to severe active RA (duration of 3 months) who had been on MTX 10 mg to 25 mg/week ≥6 weeks. Primary endpoints were reduction of signs and symptoms (ACR20) at 24 weeks, change in van der Heijde mTSS at 52 weeks, and change from baseline in HAQ-DI at 16 weeks. After week 16 in MOBILITY, patients with an inadequate response could have been treated with open-label KEVZARA 200 mg every 2 weeks.[2]

TARGET Study Design: A 24-week, randomized, double-blind, parallel group, placebo-controlled, multicenter study (N=546) assessing the efficacy and safety of KEVZARA 200 mg and 150 mg added to background conventional DMARD(s) in adult patients with moderate to severe active RA (6 months duration) with inadequate response and/or intolerance to 1 or more TNF antagonists, when administered with background conventional DMARD(s). Primary endpoints were reduction of signs and symptoms (ACR20) at 24 weeks and change from baseline in HAQ-DI at 12 weeks. After week 12 in TARGET, patients with an inadequate response could have been treated with open-label KEVZARA 200 mg every 2 weeks.[3]

TNF-IR=tumor necrosis factor inhibitor inadequate response or intolerant; MTX-IR=methotrexate inadequate response; ACR20=American College of Rheumatology 20% improvement criteria; q2w=once every 2 weeks; DMARD(s)=disease-modifying antirheumatic drug(s); MTX=methotrexate; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified total Sharp score; CI=confidence interval; TNF=tumor necrosis factor.

Ask your KEVZARA representative for more information about controlling signs and symptoms of RA

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ***Laboratory Abnormalities.*** Treatment with KEVZARA was associated with decreases in absolute neutrophil counts (including neutropenia), and platelet counts; and increases in transaminase levels and lipid parameters (LDL, HDL cholesterol, and/or triglycerides). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with KEVZARA. Assess neutrophil count, platelet count, and ALT/AST levels prior to initiation with KEVZARA. Monitor these parameters 4 to 8 weeks after start of therapy and every 3 months thereafter. Assess lipid parameters 4 to 8 weeks after start of therapy, then at 6 month intervals.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including **Boxed WARNING,** on following pages.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ***Gastrointestinal Perforation.*** GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Gastrointestinal perforations have been reported in clinical studies, primarily as complications of diverticulitis. Promptly evaluate patients presenting with new onset abdominal symptoms.
- ***Immunosuppression.*** Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with KEVZARA on the development of malignancies is not known but malignancies have been reported in clinical studies.
- ***Hypersensitivity Reactions.*** Hypersensitivity reactions have been reported in association with KEVZARA. Hypersensitivity reactions that required treatment discontinuation were reported in 0.3% of patients in controlled RA trials. Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of KEVZARA immediately. Do not administer KEVZARA to patients with known hypersensitivity to sarilumab.
- ***Active Hepatic Disease and Hepatic Impairment.*** Treatment with KEVZARA is not recommended in patients with active hepatic disease or hepatic impairment, as treatment with KEVZARA was associated with transaminase elevations.
- ***Live Vaccines.*** Avoid concurrent use of live vaccines during treatment with KEVZARA due to potentially increased risk of infections. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving KEVZARA.

ADVERSE REACTIONS

- The most common serious adverse reactions were infections. The most frequently observed serious infections included pneumonia and cellulitis. The most common adverse reactions (occurred in at least 3% of patients treated with KEVZARA + DMARDs) are neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections.

DRUG INTERACTIONS

- Exercise caution when KEVZARA is co-administered with CYP substrates with a narrow therapeutic index (e.g. warfarin or theophylline), or with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure which may reduce the activity of the CYP3A4 substrate.
- Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6Rα antagonists such as KEVZARA might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations.

USE IN SPECIFIC POPULATIONS

- KEVZARA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Because monoclonal antibodies could be excreted in small amounts in human milk, the benefits of breastfeeding and the potential adverse effects on the breastfed child should be considered along with the mother's clinical need for KEVZARA.
- There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to KEVZARA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.
- Use caution when treating the elderly.

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

KEVZARA is available by prescription only.

References: 1. KEVZARA [prescribing information]. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc. **2.** Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatol.* 2015;67(6):1424-1437. **3.** Fleischmann R, van Adelsberg J, Lin Y, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. *Arthritis Rheumatol.* 2017;69(2):277-290. **4.** Data on file, Sanofi/Regeneron. Integrated summary. April 1, 2017. **5.** Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis.* 2017;76:840-847. **6.** Humira [package insert]. North Chicago, IL: AbbVie Inc; 2019.

We have your patients covered.

Ask your KEVZARA representative about coverage support and access in your area

Please see Brief Summary of full Prescribing Information, including **Boxed WARNING,** on following pages.

SANOFI GENZYME REGENERON

SAUS.SARI.19.07.4142b

KEVZARA® **Rx Only**
(sarilumab) injection, for subcutaneous use

Brief Summary of Prescribing Information

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with KEVZARA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Opportunistic infections have also been reported in patients receiving KEVZARA. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Avoid use of KEVZARA in patients with an active infection.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before KEVZARA use and during therapy. Treatment for latent infection should be initiated prior to KEVZARA use.**
- **Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. If a serious infection develops, interrupt KEVZARA until the infection is controlled.

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.

1 INDICATIONS AND USAGE

KEVZARA® is indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

KEVZARA may be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs.

The recommended dosage of KEVZARA is 200 mg once every two weeks given as a subcutaneous injection.

Reduce dose to 150 mg once every two weeks for management of neutropenia, thrombocytopenia and elevated liver enzymes *[see Dosage and Administration (2.4), Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

2.2 General Considerations for Administration

- KEVZARA initiation is not recommended in patients with an absolute neutrophil count (ANC) less than 2000 per mm^3, platelet count less than 150,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN) *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]*.
- Prior to initiating KEVZARA, test patients for latent tuberculosis (TB). If positive, consider treating for TB prior to KEVZARA use *[see Warnings and Precautions (5.1)]*.
- Avoid using KEVZARA with biological DMARDs because of the possibility of increased immunosuppression and increased risk of infection. The concurrent use of KEVZARA with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators has not been studied.
- Avoid KEVZARA use in patients with active infections *[see Warnings and Precautions (5.1)]*.

2.3 Important Administration Instructions

- KEVZARA is intended for use under the guidance of a healthcare professional. A patient may self-inject KEVZARA or the patient's caregiver may administer KEVZARA. Provide proper training to patients and/or caregivers on the preparation and administration of KEVZARA prior to use according to the Instructions for Use (IFU).
- Allow the pre-filled syringe to sit at room temperature for 30 minutes prior to subcutaneous injection. Do not warm KEVZARA in any other way.
- If using a pre-filled pen, allow the pre-filled pen to sit at room temperature for 60 minutes prior to subcutaneous injection. Do not warm KEVZARA in any other way.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEVZARA solution should be clear and colorless to pale yellow. Do not use if the solution is cloudy, discolored or contains particles, or if any part of the pre-filled syringe or pre-filled pen appears to be damaged.
- Instruct patients to inject the full amount in the syringe or pen (1.14 mL), which provides 200 mg or 150 mg of KEVZARA, according to the directions provided in the IFU.
- Rotate injection sites with each injection. Do not inject into skin that is tender, damaged, or has bruises or scars.

2.4 Dosage Modifications for Laboratory Abnormalities or Serious Infection

If a patient develops a serious infection, hold treatment with KEVZARA until the infection is controlled.

Modify dosage in case of neutropenia, thrombocytopenia or liver enzyme elevations (see Table 1). For treatment initiation criteria, see *Dosage and Administration (2.2)*.

Table 1: KEVZARA Dosage Modification for Neutropenia, Thrombocytopenia, or Elevated Liver Enzymes

Low Absolute Neutrophil Count (ANC) *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2) in the full prescribing information]*	
Lab Value (cells/ mm^3)	**Recommendation**
ANC greater than 1000	Maintain current dosage of KEVZARA.
ANC 500–1000	Hold treatment with KEVZARA until ANC greater than 1000. KEVZARA can then be resumed at 150 mg every two weeks and increased to 200 mg every two weeks as clinically appropriate.
ANC less than 500	Discontinue KEVZARA.
Low Platelet Count *[see Warnings and Precautions (5.2)]*	
Lab Value (cells/ mm^3)	**Recommendation**
50,000–100,000	Hold treatment with KEVZARA until platelets greater than 100,000. KEVZARA can then be resumed at 150 mg every two weeks and increased to 200 mg every two weeks as clinically appropriate.
Less than 50,000	If confirmed by repeat testing, discontinue KEVZARA.
Liver Enzyme Abnormalities *[see Warnings and Precautions (5.2)]*	
Lab Value	**Recommendation**
ALT greater than ULN to 3 times ULN or less	Consider dosage modification of concomitant DMARDs as clinically appropriate.
ALT greater than 3 times ULN to 5 times ULN or less	Hold treatment with KEVZARA until ALT less than 3 times ULN. KEVZARA can then be resumed at 150 mg every two weeks and increased to 200 mg every two weeks as clinically appropriate.
ALT greater than 5 times ULN	Discontinue KEVZARA.

4 CONTRAINDICATIONS

KEVZARA is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including KEVZARA for rheumatoid arthritis (RA). The most frequently observed serious infections with KEVZARA included pneumonia and cellulitis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with KEVZARA. Some patients presented with disseminated rather than localized disease and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids, which in addition to RA may predispose them to infections. While not reported in KEVZARA clinical studies, other serious infections (e.g., histoplasmosis, cryptococcus, aspergillosis) have been reported in patients receiving other immunosuppressive agents for the treatment of RA.

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

- chronic or recurrent infection;
- a history of serious or opportunistic infections;
- underlying conditions, in addition to RA, that may predispose them to infection;
- been exposed to tuberculosis; or
- lived in or traveled to areas of endemic tuberculosis or endemic mycoses.

Closely monitor patients for the development of signs and symptoms of infection during treatment with KEVZARA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants *[see Dosage and Administration (2.4), Adverse Reactions (6.1)]*.

Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection.

Perform prompt and complete diagnostic testing appropriate for an immunocompromised patient who develops a new infection during treatment with KEVZARA; initiate appropriate antimicrobial therapy, and closely monitor the patient.

Tuberculosis

Evaluate patients for tuberculosis (TB) risk factors and test for latent infection prior to initiating treatment with KEVZARA. Treat patients with latent TB with standard antimycobacterial therapy before initiating KEVZARA. Consider anti-TB therapy prior to initiation of KEVZARA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but having risk factors for TB infection. When considering anti-TB therapy, consultation with a physician with expertise in TB may be appropriate.

Closely 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 has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with KEVZARA *[see Adverse Reactions (6.1)]*. The risk of Hepatitis B reactivation with KEVZARA is unknown since patients who were at risk for reactivation were excluded.

5.2 Laboratory Abnormalities

Neutropenia

Treatment with KEVZARA was associated with a higher incidence of decrease in absolute neutrophil count (ANC), including neutropenia *[see Adverse Reactions (6.1)]*.

- Assess neutrophil count prior to initiation of KEVZARA and monitor neutrophil count 4 to 8 weeks after start of therapy and every 3 months thereafter *[see Clinical Pharmacology (12.2) in the full prescribing information]*. For recommendations regarding initiating KEVZARA therapy and dosage modifications based on ANC results see *Dosage and Administration (2.2 and 2.4)*.
- Based on the pharmacodynamics of the changes in ANC *[see Clinical Pharmacology (12.2) in the full prescribing information]*, use results obtained at the end of the dosing interval when considering dose modification.

Thrombocytopenia

Treatment with KEVZARA was associated with a reduction in platelet counts in clinical studies *[see Adverse Reactions (6.1)]*.

- Assess platelet count prior to initiation of KEVZARA and monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommendations regarding initiating KEVZARA therapy and dosage modifications based on platelet counts see *Dosage and Administration (2.2 and 2.4)*.

Elevated Liver Enzymes

Treatment with KEVZARA was associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies *[see Adverse Reactions (6.1)]*. Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with KEVZARA.

- Assess ALT/AST levels prior to initiation of KEVZARA and monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, consider other liver function tests such as bilirubin. For recommendations regarding initiating KEVZARA therapy and dosage modifications based on transaminase elevations see *Dosage and Administration (2.2 and 2.4)*.

Lipid Abnormalities

Treatment with KEVZARA was associated with increases in lipid parameters such as LDL cholesterol, HDL cholesterol and/or triglycerides *[see Adverse Reactions (6.1)]*.

- Assess lipid parameters approximately 4 to 8 weeks following initiation of treatment with KEVZARA, then at approximately 6 month intervals.
- Manage patients according to clinical guidelines for the management of hyperlipidemia.

5.3 Gastrointestinal Perforation

Gastrointestinal perforations have been reported in clinical studies, primarily as complications of diverticulitis. GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Promptly evaluate patients presenting with new onset abdominal symptoms *[see Adverse Reactions (6.1)]*.

5.4 Immunosuppression

Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with KEVZARA on the development of malignancies is not known but malignancies were reported in clinical studies *[see Adverse Reactions (6.1)]*.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions have been reported in association with KEVZARA *[see Adverse Reactions (6.1)]*. Hypersensitivity reactions that required treatment discontinuation were reported in 0.3% of patients in controlled RA trials. Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of KEVZARA immediately. Do not administer KEVZARA to patients with known hypersensitivity to sarilumab *[see Contraindications (4) and Adverse Reactions (6.1)]*.

5.6 Active Hepatic Disease and Hepatic Impairment

Treatment with KEVZARA is not recommended in patients with active hepatic disease or hepatic impairment, as treatment with KEVZARA was associated with transaminase elevations *[see Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.

5.7 Live Vaccines

Avoid concurrent use of live vaccines during treatment with KEVZARA due to potentially increased risk of infections; clinical safety of live vaccines during KEVZARA treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving KEVZARA. The interval between live vaccinations and initiation of KEVZARA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents *[see Drug Interactions (7.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Serious infections *[see Warnings and Precautions (5.1)]*
- Neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities *[see Warnings and Precautions (5.2)]*
- Gastrointestinal perforation *[see Warnings and Precautions (5.3)]*
- Immunosuppression *[see Warnings and Precautions (5.4)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

All patients in the safety data described below had moderately to severely active rheumatoid arthritis.

The safety of KEVZARA in combination with conventional DMARDs was evaluated based on data from seven studies, of which two were placebo-controlled, consisting of 2887 patients (long-term safety population). Of these, 2170 patients received KEVZARA for at least 24 weeks, 1546 for at least 48 weeks, 1020 for at least 96 weeks, and 624 for at least 144 weeks.

The pre-rescue placebo-controlled population includes patients from the two Phase 3 efficacy studies (Studies 1 and 2) from weeks 0 to 16 for Study 1 and weeks 0 to 12 for Study 2, and was used to assess common adverse reactions and laboratory abnormalities prior to patients being permitted to switch from placebo to KEVZARA. In this population, 582 patients, 579 patients, and 579 patients received KEVZARA 200 mg, KEVZARA 150 mg, or placebo once every two weeks, respectively, in combination with conventional DMARDs.

The 52-week placebo-controlled population includes patients from one Phase 2 study of 12 week duration and two Phase 3 efficacy studies (one of 24 week duration and the other of 52 week duration). This placebo-controlled population includes all subjects from the double-blind, placebo-controlled periods from each study and was analyzed under their original randomization assignment. In this population, 661 patients, 660 patients, and 661 patients received KEVZARA 200 mg, KEVZARA 150 mg, or placebo once every two weeks, respectively, in combination with conventional DMARDs.

Most safety data are described for the pre-rescue population. For rarer events, the 52-week placebo-controlled population is used.

The most common serious adverse reactions were infections *[see Warnings and Precautions (5.1)]*.

The most frequent adverse reactions (occurring in at least 3% of patients treated with KEVZARA in combination with DMARDs) observed with KEVZARA in the clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections.

In the pre-rescue placebo-controlled population, premature discontinuation due to adverse reactions occurred in 8%, 6% and 3% of patients treated with KEVZARA 200 mg, KEVZARA 150 mg, and placebo, respectively.

The most common adverse reaction (greater than 1%) that resulted in discontinuation of therapy with KEVZARA was neutropenia.

The use of KEVZARA as monotherapy was assessed in 132 patients, of which 67 received KEVZARA 200 mg and 65 patients received KEVZARA 150 mg without concomitant DMARDs. The safety profile was generally consistent with that in the population receiving concomitant DMARDs.

Overall Infections

In the pre-rescue placebo-controlled population, the rate of infections in the 200 mg and 150 mg KEVZARA + DMARD group was 110 and 105 events per 100 patient-years, respectively, compared to 81 events per 100 patient-years in the placebo + DMARD group. The most commonly reported infections (2% to 4% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis.

In the 52-week placebo-controlled population, 0.8% of patients (5 patients) treated with KEVZARA 200 mg + DMARD, 0.6% (4 patients) treated with KEVZARA 150 mg + DMARD and 0.5% (3 patients) treated with placebo + DMARD had an event of herpes zoster *[see Warnings and Precautions (5.1)]*.

The overall rate of infections with KEVZARA + DMARD in the long-term safety population was consistent with rates in the controlled periods of the studies.

Serious Infections

In the pre-rescue population, the rate of serious infections in the 200 mg and 150 mg KEVZARA + DMARD group was 3.8 and 4.4 events per 100 patient-years, respectively, compared to 2.5 events per 100 patient-years in the placebo + DMARD group. In the 52-week placebo-controlled population, the rate of serious infections in the 200 mg and 150 mg KEVZARA + DMARD group was 4.3 and 3.0 events per 100 patient-years, respectively, compared to 3.1 events per 100 patient-years in the placebo + DMARD group.

In the long-term safety population, the overall rate of serious infections was consistent with rates in the controlled periods of the studies. The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infection have been reported *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Perforation

In the 52-week placebo-controlled population, one patient on KEVZARA therapy experienced a gastrointestinal (GI) perforation (0.11 events per 100 patient-years). In the long-term safety population, the overall rate of GI perforation was consistent with rates in the controlled periods of the studies. Reports of GI perforation were primarily reported as complications of diverticulitis including lower GI perforation and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs) or corticosteroids. The contribution of these concomitant medications relative to KEVZARA in the development of GI perforations is not known *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions

In the pre-rescue placebo-controlled population, the proportion of patients who discontinued treatment due to hypersensitivity reactions was higher among those treated with KEVZARA (0.3% in 200 mg, 0.2% in 150 mg) than placebo (0%). The rate of discontinuations due to hypersensitivity in the long-term safety population was consistent with the placebo-controlled period.

Injection Site Reactions

In the pre-rescue placebo-controlled population, injection site reactions were reported in 7% of patients receiving KEVZARA 200 mg, 6% receiving KEVZARA 150 mg, and 1% receiving placebo. These injection site reactions (including erythema and pruritus) were mild in severity for the majority of patients and necessitated drug discontinuation in 2 (0.2%) patients receiving KEVZARA.

Laboratory Abnormalities

Decreased neutrophil count

In the pre-rescue placebo-controlled population, decreases in neutrophil counts less than 1000 per mm^3 occurred in 6% and 4% of patients in the 200 mg KEVZARA + DMARD and 150 mg KEVZARA + DMARD group, respectively, compared to no patients in the placebo + DMARD groups. Decreases in neutrophil counts less than 500 per mm^3 occurred in 0.7% of patients in both the 200 mg KEVZARA + DMARD and 150 mg KEVZARA + DMARD groups. Decrease in ANC was not associated with the occurrence of infections, including serious infections.

In the long-term safety population, the observations on neutrophil counts were consistent with what was seen in the placebo-controlled clinical studies *[see Warnings and Precautions (5.2)]*.

Decreased platelet count

In the pre-rescue placebo-controlled population, decreases in platelet counts less than 100,000 per mm^3 occurred in 1% and 0.7% of patients on 200 mg and 150 mg KEVZARA + DMARD, respectively, compared to no patients on placebo + DMARD, without associated bleeding events.

In the long-term safety population, the observations on platelet counts were consistent with what was seen in the placebo-controlled clinical studies *[see Warnings and Precautions (5.2)]*.

Elevated liver enzymes

Liver enzyme elevations in the pre-rescue placebo-controlled population (KEVZARA + DMARD or placebo + DMARD) are summarized in Table 2. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as interruption of KEVZARA or reduction in dose, resulted in decrease or normalization of liver enzymes *[see Dosage and Administration (2.4)]*. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment *[see Warnings and Precautions (5.2)]*.

Table 2: Incidence of Liver Enzyme Elevations in Adults with Moderately to Severely Active Rheumatoid Arthritis*

	Placebo + DMARD N=579	KEVZARA 150 mg + DMARD N=579	KEVZARA 200 mg + DMARD N=582
AST			
Greater than ULN to 3 times ULN or less	15%	27%	30%
Greater than 3 times ULN to 5 times ULN	0%	1%	1%
Greater than 5 times ULN	0%	0.7%	0.2%
ALT			
Greater than ULN to 3 times ULN or less	25%	38%	43%
Greater than 3 times ULN to 5 times ULN	1%	4%	3%
Greater than 5 times ULN	0%	1%	1%

ULN = Upper Limit of Normal
*Phase 3 placebo-controlled safety population through the pre-rescue period

Lipid Abnormalities

Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of KEVZARA + DMARDs in the placebo-controlled population. Increases were observed at this time point with no additional increases observed thereafter. Changes in lipid parameters from baseline to Week 4 are summarized below:

- Mean LDL increased by 12 mg/dL in the KEVZARA 150 mg every two weeks + DMARD group and 16 mg/dL in the KEVZARA 200 mg every two weeks + DMARD group.
- Mean triglycerides increased by 20 mg/dL in the KEVZARA 150 mg every two weeks + DMARD group and 27 mg/dL in the KEVZARA 200 mg every two weeks + DMARD group.
- Mean HDL increased by 3 mg/dL in both the KEVZARA 150 mg every two weeks + DMARD and KEVZARA 200 mg every two weeks + DMARD groups.

In the long-term safety population, the observations in lipid parameters were consistent with what was observed in the placebo-controlled clinical studies.

Malignancies

In the 52-week placebo-controlled population, 9 malignancies (exposure-adjusted event rate of 1.0 event per 100 patient-years) were diagnosed in patients receiving KEVZARA+ DMARD compared to 4 malignancies in patients in the control group (exposure-adjusted event rate of 1.0 event per 100 patient-years).

In the long-term safety population, the rate of malignancies was consistent with the rate observed in the placebo-controlled period *[see Warnings and Precautions (5.4)]*.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on KEVZARA + DMARD and greater than those observed in patients on placebo + DMARD are summarized in Table 3.

Table 3: Common Adverse Reactions* in Adults with Moderately to Severely Active Rheumatoid Arthritis †

Preferred Term	Placebo + DMARD (N=579)	KEVZARA 150 mg + DMARD (N=579)	KEVZARA 200 mg + DMARD (N=582)
Neutropenia	0.2%	7%	10%
Alanine aminotransferase increased	2%	5%	5%
Injection site erythema	0.9%	5%	4%
Injection site pruritus	0.2%	2%	2%
Upper respiratory tract infection	2%	4%	3%
Urinary tract infection	2%	3%	3%
Hypertriglyceridemia	0.5%	3%	1%
Leukopenia	0%	0.9%	2%

*Adverse reactions occurring in 2% or more in the 150 mg KEVZARA + DMARD or 200 mg KEVZARA + DMARD groups and greater than observed in Placebo + DMARD
†Pre-rescue, placebo-controlled population

Medically relevant adverse reactions occurring at an incidence less than 2% in patients with rheumatoid arthritis treated with KEVZARA in controlled studies was oral herpes.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to sarilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the pre-rescue population, 4.0% of patients treated with KEVZARA 200 mg + DMARD, 5.7% of patients treated with KEVZARA 150 mg + DMARD and 1.9% of patients treated with placebo + DMARD, exhibited an anti-drug antibody (ADA)

response. Neutralizing antibodies (NAb) were detected in 1.0% of patients on KEVZARA 200 mg + DMARD, 1.6% of patients on KEVZARA 150 mg + DMARD, and 0.2% of patients on placebo + DMARD.
In patients treated with KEVZARA monotherapy, 9.2% of patients exhibited an ADA response with 6.9% of patients also exhibiting NAbs. Prior to administration of KEVZARA, 2.3% of patients exhibited an ADA response.
No correlation was observed between ADA development and either loss of efficacy or adverse reactions.

7 DRUG INTERACTIONS

7.1 Use with Other Drugs for Treatment of Rheumatoid Arthritis

Population pharmacokinetic analyses did not detect any effect of methotrexate (MTX) on sarilumab clearance. KEVZARA has not been investigated in combination with JAK inhibitors or biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.2)]*.

7.2 Interactions with CYP450 Substrates

Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes and therefore have the potential to alter the pharmacokinetics of concomitantly administered drugs that are substrates of these enzymes. Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6Rα antagonists such as KEVZARA might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations.
The modulation of IL-6 effect on CYP enzymes by KEVZARA may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of KEVZARA, in patients being treated with CYP substrate medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., theophylline) and adjust the individual dose of the medicinal product as needed.
Exercise caution when coadministering KEVZARA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of KEVZARA on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

7.3 Live Vaccines

Avoid concurrent use of live vaccines during treatment with KEVZARA *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to KEVZARA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.
Risk Summary
The limited human data with KEVZARA in pregnant women are not sufficient to inform drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as sarilumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero exposed infant *[see Clinical Considerations]*. From animal data, and consistent with the mechanism of action, levels of IgG, in response to antigen challenge, may be reduced in the fetus/infant of treated mothers *[see Clinical Considerations and Data]*.
In an animal reproduction study, consisting of a combined embryo-fetal and pre- and postnatal development study with monkeys that received intravenous administration of sarilumab, there was no evidence of embryotoxicity or fetal malformations with exposures up to approximately 84 times the maximum recommended human dose (MRHD) *[see Data]*. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition *[see Data]*.
The estimated background risk of major birth defects and miscarriage for the indicated population is 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 in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. KEVZARA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
Clinical Considerations
Fetal/Neonatal Adverse Reactions
Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to KEVZARA in utero *[see Warnings and Precautions (5.7)]*. From the animal data, and consistent with the mechanism of action, levels of IgG, in response to antigen challenge, may be reduced in the fetus/infant of treated mothers *[see Data]*.
Data
Animal Data
In a combined embryo-fetal and pre- and postnatal development study, pregnant cynomolgus monkeys received sarilumab at intravenous doses of 0, 5, 15, or 50 mg/kg/week from confirmation of pregnancy at gestation day (GD) 20, throughout the period of organogenesis (up to approximately GD 50), and continuing to natural birth of infants at around GD 165. Maintenance of pregnancy was not affected at any doses. Sarilumab was not embryotoxic or teratogenic with exposures up to approximately 84 times the MRHD (based on AUC with maternal intravenous doses up to 50 mg/kg/week). Sarilumab had no effect on neonatal growth and development evaluated up to one month after birth. Sarilumab was detected in the serum of neonates up to one month after birth, suggesting that the antibody had crossed the placenta.
Following antigen challenge, decreased IgG titers attributed to the immunosuppressive action of sarilumab were evident in studies with older monkeys, with exposures up to approximately 80 times the MRHD (based on AUC with intravenous doses up to 50 mg/kg/week) and juvenile mice treated with an analogous antibody, which binds to murine IL-6Rα to inhibit IL-6 mediated signaling, at subcutaneous doses up to 200 mg/kg/week. These findings suggest the potential for decreased IgG titers, following antigen challenge, in infants of mothers treated with KEVZARA.
Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 ($Il6^{-/-}$ null mice), parturition was delayed relative to wild-type ($Il6^{+/+}$) mice. Administration of recombinant IL-6 to Il6-/- null mice restored the normal timing of delivery.

8.2 Lactation

Risk Summary
No information is available on the presence of sarilumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is present in human milk. If sarilumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to sarilumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of KEVZARA to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KEVZARA and the potential adverse effects on the breastfed child from KEVZARA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of KEVZARA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in clinical studies of KEVZARA *[see Clinical Studies (14) in the full prescribing information]*, 15% were 65 years of age and over, while 1.6% were 75 years and over. In clinical studies, no overall differences in safety and efficacy were observed between older and younger patients. The frequency of serious infection among KEVZARA and placebo-treated patients 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment

The safety and efficacy of KEVZARA have not been studied in patients with hepatic impairment, including patients with positive HBV or HCV serology *[see Warnings and Precautions (5.6)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild to moderate renal impairment. KEVZARA has not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

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sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and

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Issue Date: April 2018

SAI-BPLR-SL-APR18a Revised: April 2018a

Imaging remission: A ticket to overtreatment?

BY MITCHEL L. ZOLER
REPORTING FROM EULAR 2019 CONGRESS

MADRID – Defining remission in patients with rheumatoid arthritis depends on their clinical status, not on the presence or absence of inflammatory signals on ultrasound or MRI, many rheumatologists now agree.

The strong consensus that's formed against using imaging as a criterion for RA remission was apparent at the European Congress of Rheumatology during presentation of a pending update to the EULAR recommendations for managing RA, as well as in at least two separate, invited lectures.

"Imaging is out," proclaimed Josef S. Smolen, MD, as he spoke at the congress about the pending RA management revisions. This condemnation of imaging by ultrasound or MRI as an unsafe and misleading target for RA treatment by Dr. Smolen, professor of medicine at the Medical University of Vienna, was perhaps the most forceful statement he made while presenting the draft revision of EULAR's RA recommendations.

The case for using ultrasound or MR to find inflammatory signatures in joints that can function as treatment targets collapsed earlier in 2019 with publication of results from IMAGINE-RA (An MRI-Guided Treatment Strategy to Prevent Disease Progression in Patients With Rheumatoid Arthritis), a multicenter Danish study that randomized 200 RA patients in remission to either a conventional, disease activity–guided treatment target (in this case the DAS28-CRP [Disease Activity Score in 28 joints plus C-reactive protein]), or a treatment target that included the conventional clinical target plus treating to eliminate any bone marrow edema visualized by MRI. After 24 months of treatment, the prevalence of clinical remission and MRI remission was about the same in both arms, with no statistically significant differences. But serious adverse events in 6 patients managed by their clinical assessment compared favorably against 17 among those managed to an imaging remission endpoint, a difference that strongly hinted at dangerous overtreatment of the imaging-guided patients (JAMA. 2019 Feb 5;321[5]:461-72).

The case for using ultrasound or MR to find inflammatory signatures in joints that can function as treatment targets collapsed earlier in 2019.

The failure of MRI assessment of inflammation to improve RA treatment in IMAGINE-RA came against the backdrop of two 2016 reports that documented the same limitation when using ultrasound to detect joint inflammation and guide treatment in RA patients. The TaSER (Targeting Synovitis in Early Rheumatoid Arthritis) study randomized 111 patients with newly diagnosed RA or undifferentiated arthritis to conventional disease activity assessment, to DAS28–erythrocyte sedimentation rate, or to that plus assessment by musculoskeletal ultrasound, and found no difference

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that deals with patients who do not respond to a first tumor necrosis factor (TNF) inhibitor plus methotrexate or another csDMARD, and now lists as the first option switching to a biologic or tsDMARD with a different mode of action followed by a different TNF inhibitor, a reversal of order from before when a different TNF inhibitor got first mention. This order change was a modest revision that reflected observational evidence that was modestly persuasive that switching to an agent with a different mechanism of action is often the most effective approach, Dr. Smolen said.

The new recommendations also reaffirmed the 11th recommendation from the 2016 version, which called for tapering of the biologic or tsDMARD from a patient in remission while retaining the csDMARD, usually methotrexate. Dr. Smolen cited new evidence in favor of this approach (Ann Rheum Dis. 2019 Jun;78[6]:746-53), which allowed the writing panel to upgrade the evidence supporting this recommendation to the A level. The concept of tapering down the biologic or tsDMARD for a patient in sustained remission while maintaining the csDMARD was "fully confirmed" in a recent report, he added. The writing panel also upticked its rating of the evidence in favor of cautiously tapering the csDMARD in patients who maintain remission on just a csDMARD.

One final element in the pending revision called out a newly identified safety signal: an increased risk for venous thromboembolism among patients on certain high dosages of JAK inhibitors, especially in patients with increased risk for venous thromboembolism. This new safety concern adds to the already-described increased risk for herpes zoster from JAK inhibitors, especially in Japanese and Korean populations, Dr. Smolen said. In general, more long-term safety data for JAK inhibitors are needed.

The draft update also added one new overarching principle: "Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA, and patients may require multiple, successive treatments throughout life." Overall, pending changes to the RA recommendations were limited because "the EULAR recommendations have achieved a steady state of the art" for defining whom to treat, treatment targets, and appropriate treatment strategies, Dr. Smolen said.

Dr. Smolen had been a consultant to or a speaker on behalf of several drug companies.

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Overreliance on DAS undermines rheumatoid arthritis management

BY MITCHEL L. ZOLER
REPORTING FROM EULAR 2019 CONGRESS

MADRID – Two major changes that improved rheumatoid arthritis management in recent years – the introduction of potent biologic and targeted synthetic drugs to control inflammatory disease, and the treat-to-target strategy – have also produced an unanticipated snag in the care patients receive. Their persistent comorbidities and their more atypical rheumatoid manifestations often go overlooked and untreated.

The situation has been dubbed "DAS blindness," when clinicians caring for patients with RA are so focused on a patient's disease activity score (DAS), measured by counting their swollen and tender joints (usually 28 joints to tally the DAS28 score), that they lose sight of other important features of a RA patient's disease such as pain and fatigue, Ruth Williams, MBChB, said in an invited talk at the European Congress of Rheumatology.

"There is so much focus on the DAS28 that people are blinded by it. Clinicians concentrate too much on the primary physical condition" of RA, "and they miss important functional, psychological, and social impacts of the disease," said Dr. Williams, a general-practice physician who is also a long-time RA patient who works as a patient representative and RA researcher at King's College London.

In Dr. William's extended personal experience as an RA patient (she was first diagnosed in 1966 as a child), management of the disease changed dramatically with the relatively recent, widespread adoption of the DAS28 score in routine clinical practice in Europe and the United States, migrating from its initial use in research studies. Once her clinicians began to use the DAS28 "I felt that perhaps I wasn't being seen anymore. It was just the biology of my disease

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in clinical or imaging outcomes (Ann Rheum Dis. 2016 Jun;75[6]:1043-50). The second report, ARCTIC (Aiming for Remission in Rheumatoid Arthritis), randomized 238 RA patients to either a tight RA control strategy based on DAS alone or based on DAS plus serial examination of joints with ultrasound. The results showed that, after 16-24 months on treatment, the two strategies produced no significant difference in the rates of sustained RA remission with no radiographic damage or swollen joints detected (BMJ. 2016 Aug 16;354:i4205).

The results from these three studies have shown that "not all inflammation seen by ultrasound or MR is pathological," and that "no imaging technique or biomarker has shown superiority to clinical assessment as a treat-to-target" goal, Sofia Ramiro, MD, said in a talk at the congress during which she reviewed this evidence.

"Treat-to-target that takes imaging into account is high risk because it exposes patients to overtreatment, which has costs in the broad sense, safety included," said Dr. Ramiro, a rheumatologist at Leiden (the Netherlands) University Medical Center. "I think that systematically evaluating a patient's joint with imaging won't have additional value, and is the wrong approach."

Mitchel L. Zoler/MDedge News

Dr. Sofia Ramiro: "Not all inflammation seen by ultrasound or MR is pathological."

A similar assessment came from Stefan Siebert, MD, during a separate lecture during the congress. He highlighted that use of ultrasound or MRI to guide treatment in these three studies consistently led to substantially higher rates of treatment escalation, treatment with biologics, and in two of the three studies a notable increase in serious adverse events. Treatment with a biologic drug was roughly twice as frequent in the imaging-guided arms of TaSER and ARCTIC, compared with the control arms in those studies, and in IMAGINE-RA, the use of a biologic drug occurred more than 20 times more often in the imaging arms, he noted. And in both TaSER and IMAGINE-RA the rate of serious adverse events was more than doubled in the imaging arms, compared with the controls.

"Just identifying inflammation [in a joint] is not enough to make a diagnosis. Inflammation is normal process, and finding it does not identify a pathological state," noted Dr. Siebert, a rheumatologist at the University of Glasgow. "Imaging leads to overdiagnosis and overtreatment when physicians use imaging inappropriately," he concluded.

Dr. Smolen has been a consultant to several drug companies. Dr. Ramiro has been a consultant to or speaker on behalf of AbbVie, Eli Lilly, Merck, Novartis, and Sanofi, and she has received research funding from Merck. Dr. Siebert has been a consultant to or speaker on behalf of AbbVie, Boehringer Ingelheim, Celgene, Janssen, Novartis, and UCB, and he has received research funding from Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Novartis, Pfizer, and UCB.

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Photos Mitchel L. Zoler/MDedge News

Dr. Ruth Williams: Clinicians "need to discuss with patients what remission means to them, and their objectives" from treatment.

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being noted rather than me as an individual," Dr. Williams said in an interview. Clinicians "need to discuss with patients what remission means to them, and their objectives" from treatment, because a patient's treatment goals may go beyond just reducing the number of swollen or tender joints they total in the DAS28 assessment.

Rheumatologists also have begun to recognize this common disconnect between both the assessment and the antirheumatoid treatment that RA patients routinely receive, and the symptoms that cause problems for RA patients that are not directly tied to their inflammatory disease. Patients can present with remission-level responses in their tender and swollen joint counts and in their serum level of C-reactive protein or erythrocyte sedimentation rate but still score high on the patient global assessment (PGA) scale, a residual consequence of RA that places them out of remission range based on the 2011 "Boolean" criteria for RA remission in trials endorsed by the American College of Rheumatology and European League Against Rheumatism (Arthritis Rheum. 2011 Mar;63[3]:373-86).

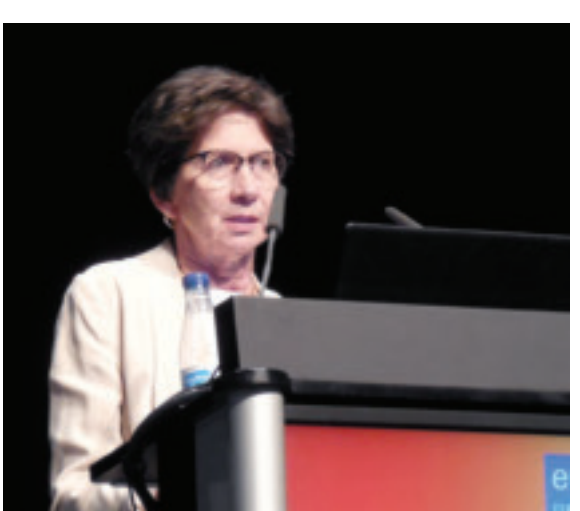
In a review of 411 RA patients who met three of the four ACR/EULAR criteria that collectively define remission, 61% missed on the PGA measure (Ann Rheum Dis. 2012 Oct;71[10]:1702-5), noted Joan M. Bathon, MD, professor of medicine and director of rheumatology at Columbia University, New York, in a talk during the Congress. Another review of 273 RA patients who missed on one of the four criteria showed 80% missing because of their PGA score (Arthritis Res Ther. 2013;15:R221). The specific clinical features that triggered high PGAs in these patients were things like fibromyalgia, back pain, anxiety, depression, and rheumatoid activity in joints not included in the DAS28 score, Dr. Bathon noted. The PGA can have poor correlation with the other three measures, but that is a strength because it reflects different dimensions of RA that are important to patients. When the PGA is discordant with the other three measures of remission, it may not make sense to try to improve it by simply using more immunosuppressive treatment.

The solution to the dilemma of what remission target to aim for when treating to target is to apply common sense to existing guidelines and recommendations and tailor management to each patient, she concluded. "The worst thing we can do is to take criteria meant for clinical trials and for patients with average scores and apply them to every individual patient," she said. Remission guidelines are good for large populations, "but we shouldn't apply them to every single patient without thinking."

A similar plea for thoughtful use of the treat-to-target model and immunomodulatory treatment came in a separate talk from Laure Gossec, MD, a professor of rheumatology at Pitie-Salpétriere Hospital and Sorbonne University in Paris.

The challenge of DAS28 is that it was a remission criteria developed by the ACR and EULAR to use in clinical trials that was co-opted for use in routine practice. Despite that, Dr. Gossec believes that DAS28 largely succeeded in this transition. "The DAS28 performs well; it has good prognostic capacity and is widely used." In her practice, Dr. Gossec relies on the DAS28 score as her primary tool to track disease status in RA patients. "It's not perfect, but I'm familiar with it, and I work with it," she said.

It's undeniable, she acknowledged, that a high PGA often stands between a patient and remission. PGA "is hard to use to guide anti-inflammatory treatment. Many patients have high PGA scores even though they have no inflammation." Discrepancies like this create a case for dual-treatment targets, both a low swollen and tender joint count and low PGA, as separate and equal treatment goals, Dr. Gossec said, an approach she and her associates proposed in a recent article (Arthritis Care Res. 2018 Mar;709[3]:369-78).



Dr. Joan M. Bathon: Remission guidelines are good for large populations, "but we shouldn't apply them to every single patient without thinking."

Dr. Williams had no disclosures. Dr. Bathon has been a consultant to AbbVie and has received research funding from Bristol-Myers Squibb and Pfizer. Dr. Gossec has been a consultant to and has received research funding from several companies.

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Vagus nerve stimulation for rheumatology? Maybe

BY M. ALEXANDER OTTO

Vagus nerve stimulation – an established treatment for refractory epilepsy and depression – is slowly gaining momentum in rheumatology.

The work is being led by SetPoint Medical, a small company in Valencia, Calif., just north of Los Angeles. Its vagus nerve stimulation (VNS) device, dubbed the microregulator, has been implanted in 14 patients with refractory rheumatoid arthritis in the company's initial safety study.

The microregulator is a small lithium ion battery encased in an inert silastic pod; it's surgically implanted to sit atop the vagus nerve in the left side of the neck, and delivers an electrical pulse at set intervals. Data from the 12-week, sham-controlled safety study are set to be unblinded in coming weeks. (Editor's note: The results from this safety study were presented at the European Congress of Rheumatology in June 2019. See sidebar article on page 16.) A pivotal trial also is in the works, perhaps to start in late 2019, according to rheumatologist and SetPoint's Chief Medical Officer David Chernoff, MD.

Although SetPoint is ahead of the pack, it's not alone. ElectroCore, a biotech company in Basking Ridge, N.J., has expressed interest in pursuing rheumatoid arthritis and Sjögren's syndrome indications for its gammaCore device, a vagus nerve stimulator patients apply to the neck. It's already on the market for migraines and cluster headaches.

Researchers recently reported a small decrease in 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP) results after 16 RA patients with flares used the device for 4 days (Ann Rheum Dis. 2018;77:1401, Abstract AB0481). In another recent open-label study, 15 women with Sjögren's reported less fatigue while using the device for a month (Arthritis Rheumatol. 2017;69[suppl 10], Abstract 563).

Meanwhile, The Feinstein Institute for Medical Research, based in Manhasset, N.Y., on Long Island, recently reported positive outcomes in 18 patients with systemic lupus erythematosus, using its own novel device, which stimulates the vagus nerve through the earlobe. VNS was delivered for 5 minutes per day for 4 days (Arthritis Rheumatol. 2018;70[suppl 10], Abstract 2652).

Courtesy Dr. Norman B. Gaylis

Dr. Norman B. Gaylis discusses VNS device placement with a patient.

On day 5, patients who received VNS, versus sham patients in whom the device was not turned on, had a significant decrease in pain, fatigue, and joint scores. The investigators concluded that "additional studies evaluating this promising intervention and its potential mechanisms are warranted."

"We are clearly ahead of everybody because we've already implanted people, but I think it's good for the field if more people are chasing this. The more resources that are put into it, the more we can show that this approach actually works," said SetPoint's Dr. Chernoff.

The hope

In general, interest in VNS for rheumatology is being driven by the possibility that it may reduce proinflammatory cytokines, which opens the door for VNS as an alternative to biologics. The hope is that, instead of going after tumor necrosis factor and other cytokines one at a time, VNS could be used to target a range of cytokines all at once, without the cost and side effects of biologics.

"It seems so dramatically different" from what rheumatologists have done in the past, "that our first instinct is to say 'oh, that's ridiculous,' but the science behind it is actually not bad. There may indeed be something to this," said rheumatologist Joel Kremer, MD, Pfaff Family Professor of Medicine at Albany (N.Y.) Medical College.

Dr. Kremer reviewed SetPoint's early scientific data after being asked by the company to participate in the safety study; he declined for logistical reasons.

He noted that "there are some strange interactions between the CNS and inflammatory disease." When RA patients have a stroke, for instance, RA goes into remission on the side of their body affected by the stroke. "That's been known for decades, but we really don't understand what's going on there," Dr. Kremer said.

The evidence

Perhaps the strongest evidence to date for VNS as a cytokine blocker in rheumatology comes from an open-label, 12-week study, also conducted by SetPoint, in 17 patients with active RA despite methotrexate treatment; some had failed biologics (Proc Natl Acad Sci U S A. 2016 Jul 19;113[29]:8284-9. doi: 10.1073/pnas.160563511).

The microregulator wasn't ready yet, so investigators implanted a VNS system commercially available for epilepsy and reprogrammed it to deliver

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a 60-second pulse once a day to the left cervical vagus nerve, which was increased after a month to four 60-second stimulations a day in nonresponders.

The investigators "observed that TNF production in cultured peripheral blood obtained ... on day 42 was significantly reduced from" 21 days before the study was started (TNF 2,900 pg/mL on day –21, versus 1,776 pg/mL on day 42; *P* less than .05).

When VNS was shut off, TNF production increased; when it was turned back on, it dropped. Interleukin-6 also fell significantly among responders. Overall, DAS28-CRP scores fell about 1.5 points on the 10-point scale from baseline to week 12.

Two-year outcomes were recently reported (Ann Rheum Dis. 2018;77:981-2, Abstract SAT0240). All 17 patients elected to continue treatment after the initial 12 weeks. Biologics were added in nine subjects (53%), because of no or limited response to VNS. Investigators were free to change the VNS dosing regimen, which varied during the study extension up to eight 60-second bursts a day. The roughly 1.5-point improvement in DAS28-CRP was maintained at 2 years.

"These long-term data suggest that bioelectronic therapy may be used as an alternative to, or in combination with,

Continued on following page

Refractory RA responds to vagus nerve stimulation

BY SARA FREEMAN
REPORTING FROM EULAR 2019 CONGRESS

MADRID – Electrically stimulating the vagus nerve produced clinically meaningful responses in disease activity measures in patients with refractory RA in a small safety study.

Results of the first in-human study with the device were presented by Mark C. Genovese, MD, professor of medicine and director of the rheumatology clinic in the division of immunology and rheumatology at Stanford (Calif.) University, during the late-breaking clinical trials session at the European Congress of Rheumatology. He described how a total of 14 patients had the device implanted, the first 3 of whom received once-daily, open-label neurostimulation. The remaining 11 patients were randomized to either once-daily or four-times-daily neurostimulation via the device, or to receive sham therapy in which the device was implanted but not switched on. The patients had moderate to severe RA, defined as four or more tender joints, four or more swollen joints, and a Clinical Disease Activity Index (CDAI) score greater than 10, plus they had radiologically active disease and an insufficient response to at least two biologic or targeted synthetic disease-modifying antirheumatic drugs with differing mechanisms of action.


Dr. Genovese

All patients went through the same schedule of device charging and they did not know if they were in the active or sham groups. At the end of the study, patients had the option to continue in a long-term safety extension phase, have the device switched off, or have it surgically removed.

A minimal clinically important difference in the 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP) and the CDAI at 12 weeks was achieved or exceeded by 5 out of 10 patients; with 2 patients achieving DAS28-CRP–defined remission.

The disease activity scores also were paired with MRI scans and showed, in a handful of individuals, that there was improvement in erosions in those with a clinical response. Greater reductions in proinflammatory cytokines – interleukin (IL)-1-beta, IL-6, IL-17, IL-23, and tumor necrosis factor – were seen with neurostimulation, compared with a sham control group.

"The reason for choosing refractory patients is, one, there's a clear unmet need, but two, because this was a first-in-human study using a novel microregulatory device stimulating the vagus nerve, we thought the benefits-to-risk ratio was most appropriate for its first trial in patients with refractory disease," Dr. Genovese explained in an interview at the meeting.

He added: "Over time, if the device proves successful for modulating disease, one can see it potentially being used earlier in the disease. Whether it is developed as a standalone or used as an adjunct on additional therapy will have to be determined based on both its efficacy and its safety."

While "there were no device or treatment-related serious adverse events," there were some "surgical complications associated with the initial procedure." One patient experienced paralysis of the left vocal cord during implantation that later resolved, and others experienced the following: Horner's syndrome, tenderness and swelling at the surgical site, acute postoperative pain, and rash and pruritus. That said, there were no withdrawals from the study due to adverse events.

Dr. Genovese disclosed receiving consulting fees from and having contracts with/grants with the company and acting as a consultant to Galvani and Vorso. He has also received research support from and served as a consultant to Sanofi/Genzyme, Genentech/Roche, and R-Pharm.

SOURCE: Genovese MC et al. Ann Rheum Dis. Jun 2019;78(Suppl 2):264, Abstract LB0009. doi: 10.1136/annrheum-dis-2019-eular.8716.

Rituximab serious infection risk predicted by immunoglobulin levels

BY SARA FREEMAN
FROM ARTHRITIS & RHEUMATOLOGY

Monitoring immunoglobulin (Ig) levels at baseline and before each cycle of rituximab could reduce the risk of serious infection events (SIEs) in patients needing repeated treatment, according to research published in Arthritis & Rheumatology.

In a large, single-center, longitudinal study conducted at a tertiary referral center, having low IgG (less than 6 g/L) in particular was associated with a higher rate of SIEs, compared with having normal IgG levels (6-16 g/L). Among 103 of 700 patients who had low levels of IgG before starting treatment with rituximab for various rheumatic and musculoskeletal diseases (RMDs), there were 16.4 SIEs per 100 patient-years. In those who developed low IgG during subsequent cycles of rituximab therapy, the SIE rate was even higher, at 21.3 per 100 patient-years. By comparison, the SIE rate for those with normal IgG levels was 9.7 per 100 patient-years.

"We really have to monitor immunoglobulins at baseline and also before we re-treat the patients, because higher IgG level is protective of serious infections," study first author Md Yuzaiful Md Yusof, MBChB, PhD, said in an interview.

Low IgG has been linked to a higher risk of SIEs in the first 12 months of rituximab therapy, but until now, there have been limited data on infection predictors during repeated cycles of treatment. While IgG is a consistent marker of SIEs associated with repeated rituximab treatment, IgM and IgA should also be monitored to give a full picture of any hyperglobulinemia that may be present.

"There is no formal guidance on how to safely monitor patients on rituximab," observed Dr. Md Yusof, who will present these data at the 2019 European Congress of Rheumatology in Madrid. The study's findings could help to change that, however, as they offer a practical way to help predict and thus prevent SIEs. The study's findings not only validate previous

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biological[s]," concluded Dr. Chernoff and other study team members.

The next steps

When asked for comment, Daniel E. Furst, MD, professor of medicine (emeritus) at the University of California, Los Angeles, said "there certainly are neurotropic factors" at play in rheumatology, "so there's sort of a potential reason why" VNS might work, "but we need to understand far more about its mechanism, and [remember] that open-label studies are not to be believed until" large, randomized, blinded, placebo-controlled studies are done.

Dr. Furst also is an adjunct professor at the University of Washington, Seattle, and a research professor at the University of Florence (Italy). He is in part-time practice in Los Angeles and Seattle.

If everything works out, however, "the vagus nerve may give us a much wider opportunity to block a host of cytokines; it may change the whole paradigm of how we manage rheumatoid arthritis. I think this is possibly a groundbreaking new therapeutic area, much in the way the biologics were" 20 years ago, said rheumatologist Norman B. Gaylis, MD.

Several of the 14 patients in SetPoint's safety study were enrolled at Dr. Gaylis's practice in Aventura, Fla., just north of Miami. If clinical response in that study and others correlates with a cytokine response, "that's going to be big, and very significant" in the rheumatology community, he said.

> "The vagus nerve may give us a much wider opportunity to block a host of cytokines; it may change the whole paradigm" of how we treat RA.

SetPoint's microregulator is charged wirelessly through a collar patients wear for a few minutes once a week. Dosing can also be adjusted through the collar with the help of a computer application.

The device wasn't turned on in 4 of the 14 patients in the safety study, as a sham control, but shamming was problematic because patients can potentially feel VNS as a buzz or a change in their voice. To get around that potential confounder, investigators told both sham and treated patients they might or might not feel something during the study.

Implantation takes about an hour, and is much less complex than implanting currently available epilepsy VNS systems, which require implantation of both a power source on the chest wall and wire coils on the vagus nerve.

Cardiac concerns are the main safety issue with VNS, beyond the surgery itself. Cardiac monitoring was done in the safety study to "ensure that we did not cause things like bradycardia, heart block, syncope, etc." Dr. Chernoff said. So far, they haven't turned out to be a problem.

Dr. Furst and Dr. Kremer had no relevant disclosures. Dr. Gaylis was compensated by SetPoint for participating in the safety study; he is a consultant and investigator for Electrocore. Dr. Furst and Dr. Gaylis are members of the editorial advisory board for Rheumatology News.

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work, he noted, but also add new insights into why some patients treated with repeat rituximab cycles but not others may experience a higher rate of such infections.

Altogether, the investigators examined data on 700 patients with RMDs treated with rituximab who were consecutively seen during 2012-2017 at Dr. Md Yusof's institution – the Leeds (England) Institute of Rheumatic and Musculoskeletal Medicine, which is part of the University of Leeds. Their immunoglobulin levels had been measured before starting rituximab therapy and every 4-6 months after each cycle of rituximab treatment.

Patients with any RMD being treated with at least one cycle of rituximab were eligible for inclusion in the retrospective study, with the majority (72%) taking it for rheumatoid arthritis and some for systemic lupus erythematosus (13%) or antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (7%).

One of the main aims of the study was to look for predictors of SIEs during the first 12 months and during repeated cycles of rituximab. Dr. Md Yusof and his associates also looked at how secondary hypogammaglobulinemia might affect SIE rates and the humoral response to vaccination challenge and its persistence following treatment discontinuation. Their ultimate aim was to see if these findings could then be used to develop a treatment algorithm for rituximab administration in RMDs.

Over a follow-up period encompassing 2,880 patient-years of treatment, 281 SIEs were recorded in 176 patients, giving a rate of 9.8 infections per 100 patient-years. Most (61%) of these were due to lower respiratory tract infections.

The proportion of patients experiencing their first SIE increased with time: 16% within 6 weeks of starting rituximab therapy, 35% at 12 weeks, 72% at 26 weeks, 83% at 38 weeks, and 100% by 1 year of repeated treatment.

Multivariable analysis showed that the presence of several comorbidities at baseline – notably chronic obstructive pulmonary disease, diabetes, heart failure, and prior cancer – raised the risk for SIEs with repeated rituximab therapy. The biggest factor, however, was a history of SIEs – with a sixfold increased risk of further serious infection.

Courtesy Dr. Md Yuzaiful Md Yusof

Dr. Md Yuzaiful Md Yusof: "We really have to monitor immunoglobulins at baseline and also before we re-treat the patients."

Higher corticosteroid dose and factors specific to rituximab – low IgG, neutropenia, high IgM, and a longer time to retreatment – were also predictive of SIEs.

"Low IgG also results in poor humoral response to vaccination," Dr. Md Yusof said, noting that the IgG level remains below the lower limit of normal for several years after rituximab is discontinued in most patients.

In the study, 5 of 8 (64%) patients had impaired humoral response to pneumococcal and haemophilus following vaccination challenge and 4 of 11 patients had IgG normalized after switching to another biologic disease-modifying antirheumatic drug (bDMARD).

Cyclophosphamide is commonly used as a first-line agent to induce remission in patients with severe and refractory systemic lupus erythematosus and ANCA-associated vasculitis, with patients switched to rituximab at relapse. The effect of this prior treatment was examined in 20 patients in the study, with a marked decline in almost all immunoglobulin classes seen up to 18 months. Prior treatment with immunosuppressants such as intravenous cyclophosphamide could be behind progressive reductions in Ig levels seen with repeated rituximab treatment rather than entirely because of rituximab, Dr. Md Yusof said.

Dr. Md Yusof, who is a National Institute for Health Research (NIHR) Academic Clinical Lecturer at the University of Leeds, said the value of the study, compared with others, is that hospital data for all patients treated with rituximab with at least 3 months follow-up were included, making it an almost complete data set.

"By carefully reviewing records of every patient to capture all infection episodes in the largest single-center cohort study to date, our findings provide insights on predictors of SIEs as well as a foundation for safety monitoring of rituximab," he and his coauthors wrote.

They acknowledge reporting a higher rate of SIEs than seen in registry and clinical studies with rituximab, which may reflect a "channeling bias" as the patients comprised those with multiple comorbidities including those that represent a relative contraindication for bDMARD use. That said, the findings clearly show that Ig levels should be monitored before and after each rituximab cycle, especially in those with comorbid diseases and those with low IgG levels to start with.

They conclude that an "individualized benefit-risk assessment" is needed to determine whether rituximab should be repeated in those with low IgG as this is a "consistent predictor" of SIE and may "increase infection profiles when [rituximab] is switched to different bDMARDs."

The research was supported by Octapharma, the National Institute for Health Research (NIHR), and NIHR Leeds Biomedical Research Centre based at Leeds Teaching Hospitals NHS Trust in England. Dr. Md Yusof had no conflicts of interest. Several coauthors disclosed financial ties to multiple pharmaceutical companies, including Roche.

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SOURCE: Md Yusof MY et al. Arthritis Rheumatol. 2019 May 27. doi: 10.1002/art.40937.

Lymphoma rate in RA patients is falling

BY BRUCE JANCIN
REPORTING FROM RWCS 2019

MAUI, HAWAII – The incidence of lymphoma in patients with RA appears to have been dropping during the past 2 decades – and for rheumatologists, that's news you can use.

"I think this is encouraging data about where we're headed with therapy. And it's encouraging data for your patients, that maybe more effective therapies can lead to a lower risk of cancer," John J. Cush, MD, commented at the 2019 Rheumatology Winter Clinical Symposium.

"Patients are always worried about cancer," observed symposium director Arthur Kavanaugh, MD. "I think this is very useful data to bring to a discussion with patients."

Bruce Jancin/MDedge News

Dr. John J. Cush (left) and Dr. Arthur Kavanaugh answer questions at the conference. "Does this [lower lymphoma rate] reflect a change in the practice of rheumatology? I think it does," Dr. Cush said.

The study they highlighted was presented at the 2018 annual meeting of the American College of Rheumatology by Namrata Singh, MD, of the University of Iowa, Iowa City, and coinvestigators from Veterans Affairs medical centers around the country. They analyzed the incidence of lymphomas as well as all-site cancers in 50,870 men with RA in the national VA health care system during 2001-2015 and compared the rates with the background rates in the general U.S. population as captured in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

The key finding: While the standardized incidence ratio for the development of lymphoma in the RA patients during 2001-2005 was 190% greater than in the SEER population, the SIR dropped to 1.6 in 2006-2010 and stayed low in 2011-2015.

"These are the only data I'm aware of that say maybe lymphomas are becoming less frequent among RA patients," said Dr. Kavanaugh, professor of medicine at the University of California, San Diego.

Historically, RA has been associated with roughly a 100% increased risk of lymphoma. The source of the increased risk has been a matter of controversy: Is it the result of immunostimulation triggered by high RA disease activity, or a side effect of the drugs employed in treatment of the disease? The clear implication of the VA study is that it's all about disease activity.

"The lymphoma rate is higher early in the use of our new therapies, in 2001-2005, because the patients who went on TNF [tumor necrosis factor] inhibitors then had the most disease activity. But with time, patients are getting those treatments earlier. Does this [lower lymphoma rate] reflect a change in the practice of rheumatology? I think it does," according to Dr. Cush, professor of medicine and rheumatology at Baylor University Medical Center, Dallas.

Dr. Kavanaugh agreed. "Now, if we're treating early and treating to target, we should see less lymphomas than we did back in the day."

The rate of cancers at all sites in the VA RA patients has been going down as well, with the SIR dropping from 1.8 in 2001-2005 to close to 1, the background rate in the general population.

"What's great about this study is this is a large data set. You really can't compare an RA population on and off treatment. The right comparison is to a normal population – and SEER accounts for something like 14% of the U.S. population," Dr. Cush said.

Previous support for the notion that the increased lymphoma risk associated with RA was a function of disease activity came from a Swedish study of 378 RA patients in the prebiologic era who developed lymphoma and a matched cohort of 378 others without lymphoma. The investigators found that patients with moderate overall RA disease activity were at a 700% increased risk of lymphoma, compared with those with low overall disease activity, and that patients with high RA disease activity were at a 6,900% increased risk (Arthritis Rheum. 2006 Mar;54[3]:692-701). But that was a cross-sectional study, whereas the VA study examined trends over time.

The VA RA cohort had a mean age of 64 years. About 60% were current or ex-smokers, 65% were positive for rheumatoid factor, and 62% were positive for anticyclic citrullinated peptide.

Dr. Kavanaugh said that, because of the potential for referral bias in the VA study, he's eager to see the findings reproduced in another data set.

Both Dr. Cush and Dr. Kavanaugh reported serving as a consultant to and/or receiving research funding from numerous pharmaceutical companies.

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Not an actual patient. Pill not to scale.

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ACR20 response rate for XELJANZ 5 mg BID (n=243) at month 3 (primary endpoint) was 59% vs 26% with placebo (n=122); $P<0.0001$[1,2]

PsA: OPAL Broaden (csDMARD-IR patients)

ACR20 response rate for XELJANZ 5 mg BID + csDMARD (n=107) at month 3 (primary endpoint) was 50% vs 33% with placebo + csDMARD (n=105); $P\leq0.05$[1,4,a]

See study designs on the following pages.

[a]Nonresponder imputation was applied to missing sign/symptom data.[1,4]

INDICATIONS

Rheumatoid Arthritis

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

Psoriatic Arthritis

- XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs).
- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis

- XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or who are intolerant to TNF blockers.
- Limitations of Use: Use of XELJANZ in combination with biologic therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

XELJANZ XR is not approved for use in UC.

PsA | RA | UC

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

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- More than 159,700 patients for RA, more than 6900 patients for PsA, and more than 6000 for UC

[b]Based on US data source: IQVIA Lifelink Patient Data, including Rx, Dx, and Specialty Pharmacy, June 2019.[2]

Among US rheumatologists, the **3rd most prescribed** self-administered RA advanced therapy treatment[c] since 2015 (behind adalimumab and etanercept)[2,d]

[c]Advanced therapy treatment includes abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, sarilumab, tocilizumab, and tofacitinib.[2]

[d]Internal calculations by Pfizer based on IQVIA database, US National Prescription Audit (NPA), of total prescription (TRx) products indicated for RA, July 2019.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

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

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

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

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

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

MORTALITY

Rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers in a large, ongoing, postmarketing safety study. XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not recommended for the treatment of RA or PsA. For UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

MALIGNANCIES

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

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy.

Malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily dosing in the UC long-term extension study.

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

THROMBOSIS

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, has been observed at an increased incidence in RA patients who were 50 years of age and older with at least one CV risk factor treated with XELJANZ 10 mg twice daily compared to XELJANZ 5 mg twice daily or TNF blockers in a large, ongoing postmarketing safety study. Many of these events were serious and some resulted in death.

ACR=American College of Rheumatology; BID=twice daily; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DMARD=disease-modifying antirheumatic drug; Dx=diagnosis; FDA=US Food and Drug Administration; IR=inadequate responder; JAK=Janus kinase; JAKi=Janus kinase inhibitor; PsA=psoriatic arthritis; RA=rheumatoid arthritis; Rx=prescription; UC=ulcerative colitis.

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

Study Designs

ORAL Solo (Study RA-I)[3]

A 6-month, randomized, double-blind, placebo-controlled, multicenter trial in which 610 patients with moderately to severely active RA who had an inadequate response or toxicity to a DMARD of any type received XELJANZ 5 mg BID or 10 mg BID or placebo (XELJANZ 10 mg BID is not approved for RA). Stable low-dose oral glucocorticoids allowed. All DMARDs were washed out before baseline visit, except stable doses of antimalarial agents were permitted (XELJANZ 5 mg 19%; placebo 12%). **The 3 coprimary endpoints were ACR20 response rate, HAQ-DI change, and rate of DAS28-4(ESR) <2.6 at month 3. Nonresponder imputation was applied to missing sign/symptom data.**

OPAL Broaden (Study PsA-I)[1,2,4]

A 12-month, randomized, double-blind, double-dummy, active-controlled, placebo-controlled, multicenter, phase 3 trial in which 422 adult patients with active PsA who had inadequate response to at least one csDMARD and were TNFi-naïve received either XELJANZ 5 mg BID, XELJANZ 10 mg BID, adalimumab 40 mg SC q 2 wk, or placebo. At month 3, all patients randomized to placebo were advanced to XELJANZ 5 mg BID or XELJANZ 10 mg BID in a blinded manner based on their initial randomization sequence (XELJANZ 10 mg BID is not approved for PsA). Across all treatment arms, all patients were required to receive a stable dose of one csDMARD (also known as a nonbiologic DMARD, which included methotrexate, sulfasalazine, and leflunomide). Stable low-dose oral glucocorticoids were allowed. The primary endpoints were ACR20 response rate and change from baseline in HAQ-DI score at month 3. To control for type I error at the 5% level for primary and certain secondary endpoints, statistical testing was performed for XELJANZ in a hierarchical sequence and was stopped at any point wherever statistical significance was not reached. **Study PsA-I was not designed to demonstrate noninferiority or superiority of XELJANZ to adalimumab.**

IMPORTANT SAFETY INFORMATION (cont'd)

THROMBOSIS (cont'd)

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

GASTROINTESTINAL PERFORATIONS

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

HYPERSENSITIVITY

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

LABORATORY ABNORMALITIES

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

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

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

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

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

VACCINATIONS

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

PATIENTS WITH GASTROINTESTINAL NARROWING

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

HEPATIC and RENAL IMPAIRMENT

Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

For patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 5 mg twice daily, reduce to XELJANZ 5 mg once daily.

For UC patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 10 mg twice daily, reduce to XELJANZ 5 mg twice daily.

ADVERSE REACTIONS

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

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

USE IN PREGNANCY

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

ACR=American College of Rheumatology; BID=twice daily; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-4(ESR)=Disease Activity Score for 28-joint counts based on erythrocyte sedimentation rate; DMARD=disease-modifying antirheumatic drug; HAQ-DI=Health Assessment Questionnaire–Disability Index; PsA=psoriatic arthritis; q 2 wk=every 2 weeks; RA=rheumatoid arthritis; SC=subcutaneously; TNFi=tumor necrosis factor inhibitor.

References: 1. XELJANZ/XELJANZ XR [prescribing information]. New York, NY: Pfizer Inc.; August 2019. **2.** Data on file. Pfizer Inc., New York, NY. **3.** Fleischmann R, Kremer J, Cush J, et al; for the ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med.* 2012;367(6):495-507. **4.** Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med.* 2017;377(16):1537-1550.

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

XELJANZ®
(tofacitinib)
5 mg tablets

XELJANZ® (tofacitinib)/XELJANZ® XR (tofacitinib)

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

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, AND THROMBOSIS

SERIOUS INFECTIONS Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

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

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

MORTALITY Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers in a large, ongoing, postmarketing safety study.

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

THROMBOSIS Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, has been observed at an increased incidence in rheumatoid arthritis patients who were 50 years of age and older with at least one CV risk factor treated with XELJANZ 10 mg twice daily compared to XELJANZ 5 mg twice daily or TNF blockers in a large, ongoing postmarketing safety study. Many of these events were serious and some resulted in death. Avoid XELJANZ/XELJANZ XR in patients at risk. Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis.

For patients with ulcerative colitis, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

INDICATIONS AND USAGE

Rheumatoid Arthritis XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

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

Psoriatic Arthritis XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs).

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

Ulcerative Colitis XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or who are intolerant to TNF blockers.

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

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

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

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

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

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

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

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

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

Mortality Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers in a large, ongoing, postmarketing safety study.

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

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

Malignancy and Lymphoproliferative Disorders Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy. Malignancies were observed in clinical studies of XELJANZ.

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.

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

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in XELJANZ-treated patients. In the long-term extension study, malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily.

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

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

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

Thrombosis Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, was observed at an increased incidence in patients with rheumatoid arthritis 50 years of age and older with at least one CV risk factor treated with XELJANZ 10 mg twice daily compared to XELJANZ 5 mg twice daily or TNF blockers in a large, ongoing postmarketing study. Many of these events were serious and some resulted in death.

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

- Serious Infections
- Mortality
- Malignancy and Lymphoproliferative Disorders
- Thrombosis
- Gastrointestinal Perforations
- Hypersensitivity

- Laboratory Abnormalities

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

Rheumatoid Arthritis The clinical studies described in the following sections were conducted using XELJANZ. Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

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

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

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

The most common serious adverse reactions were serious infections.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Laboratory Abnormalities

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

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

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

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

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

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

Liver Enzyme Elevations Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with XELJANZ. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalization of liver enzymes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Blood and lymphatic system disorders: Anemia

Infections and infestations: Diverticulitis

Metabolism and nutrition disorders: Dehydration

Psychiatric disorders: Insomnia

Nervous system disorders: Paresthesia

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

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

Hepatobiliary disorders: Hepatic steatosis

Skin and subcutaneous tissue disorders: Rash, erythema, pruritus

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

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

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

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

Psoriatic Arthritis XELJANZ 5 mg twice daily and 10 mg twice daily were studied in 2 double-blind Phase 3 clinical trials in patients with active psoriatic arthritis (PsA). Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily. The recommended dose for XELJANZ XR is 11 mg once daily. A dosage of XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not recommended for the treatment of PsA.

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

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

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

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

Ulcerative Colitis XELJANZ has been studied in patients with moderately to severely active UC in 4 randomized, double-blind, placebo-controlled trials (UC-I, UC-II, UC-III, and dose ranging UC-V) and an open-label long term extension study (UC-IV). Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials were: nasopharyngitis, elevated

cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Induction Trials (Study UC-I, UC-II, and UC-V):

Common adverse reactions reported in ≥2% of patients treated with XELJANZ 10 mg twice daily and ≥1% greater than that reported in patients receiving placebo in the 3 induction trials were: headache, nasopharyngitis, elevated cholesterol levels, acne, increased blood creatine phosphokinase, and pyrexia.

Maintenance Trial (Study UC-III):

Common adverse reactions reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported in patients receiving placebo are shown in the table below.

Common Adverse Reactions* in UC Patients during the Maintenance Trial (Study UC-III)

Preferred Term	XELJANZ 5 mg Twice Daily N = 198 (%)	XELJANZ 10 mg Twice Daily N = 196 (%)	Placebo N = 198 (%)
Nasopharyngitis	10	14	6
Elevated cholesterol levels**	5	9	1
Headache	9	3	6
Upper respiratory tract infection	7	6	4
Increased blood creatine phosphokinase	3	7	2
Rash	3	6	4
Diarrhea	2	5	3
Herpes zoster	1	5	1
Gastroenteritis	3	4	3
Anemia	4	2	2
Nausea	1	4	3

* reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported for placebo.

** includes hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed more often in patients treated with XELJANZ 10 mg twice daily. Four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer.

Dose-dependent adverse reactions seen in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections, serious infections, and NMSC.

Postmarketing Experience *Immune system disorders:* Drug hypersensitivity (events such as angioedema and urticaria have been observed).

DRUG INTERACTIONS

The table below includes drugs with clinically important drug interactions when administered concomitantly with XELJANZ/XELJANZ XR and instructions for preventing or managing them.

Clinical Relevant Interactions Affecting XELJANZ and XELJANZ XR When Coadministered with Other Drugs

Strong CYP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/ XELJANZ XR is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/ XELJANZ XR is recommended
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to tofacitinib and may result in loss of or reduced clinical response
Intervention	Coadministration with XELJANZ/ XELJANZ XR is not recommended
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Clinical Impact	Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis, or UC.
Intervention	Coadministration with XELJANZ/ XELJANZ XR is not recommended

USE IN SPECIFIC POPULATIONS

All information provided in this section is applicable to XELJANZ and XELJANZ XR as they contain the same active ingredient (tofacitinib).

Pregnancy

Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to XELJANZ/XELJANZ XR during pregnancy. Patients should be encouraged to enroll in the XELJANZ/XELJANZ XR pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call the toll free number 1-877-311-8972.

Risk Summary Available data with XELJANZ/XELJANZ XR use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy *(see Clinical Considerations)*. In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the recommended dose of 5 mg twice daily and approximately 36 times the maximum recommended dose of 10 mg twice daily, respectively *(see Data)*.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Data

Animal Data In a rat embryofetal developmental study, in which pregnant rats received tofacitinib during organogenesis, tofacitinib was teratogenic at exposure levels approximately 146 times the recommended dose of 5 mg twice daily, and approximately 73 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the recommended dose of 5 mg twice daily, and approximately 29 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily, and approximately 6.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg twice daily, and approximately 1.5 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats that received tofacitinib from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily, and approximately 36 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats).

Lactation

Risk Summary There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with XELJANZ/XELJANZ XR, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of XELJANZ or 36 hours after the last dose of XELJANZ XR (approximately 6 elimination half-lives).

Data

Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured.

Females and Males of Reproductive Potential

Contraception *Females* In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility *Females* Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible.

Pediatric Use The safety and effectiveness of XELJANZ/ XELJANZ XR in pediatric patients have not been established.

Geriatric Use Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65. Of the 1156 XELJANZ treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients.

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Use in Diabetics

As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes.

Renal Impairment

Moderate and Severe Impairment

XELJANZ-treated patients with moderate or severe renal impairment had greater tofacitinib blood concentrations than XELJANZ-treated patients with normal renal function. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis).

- Rheumatoid arthritis and psoriatic arthritis patients with moderate or severe renal impairment receiving XELJANZ XR should switch to XELJANZ and adjust the dosage.

Mild impairment

No dosage adjustment is required in patients with mild renal impairment.

Hepatic Impairment

Severe Impairment

XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

Moderate Impairment

XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib blood concentration than XELJANZ-treated patients with normal hepatic function. Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate hepatic impairment.

- Rheumatoid arthritis and psoriatic arthritis patients receiving XELJANZ XR should switch to XELJANZ and adjust the dosage.

Mild Impairment

No dosage adjustment of XELJANZ/XELJANZ XR is required in patients with mild hepatic impairment.

Hepatitis B or C Serology

The safety and efficacy of XELJANZ/XELJANZ XR have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

OVERDOSAGE

There is no specific antidote for overdose with XELJANZ/ XELJANZ XR. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.

In a study in subjects with end stage renal disease (ESRD) undergoing hemodialysis, plasma tofacitinib concentrations declined more rapidly during the period of hemodialysis and dialyzer efficiency, calculated as dialyzer clearance/blood flow entering the dialyzer, was high [mean (SD) = 0.73 (0.15)]. However, due to the significant non-renal clearance of tofacitinib, the fraction of total elimination occurring by hemodialysis was small, and thus limits the value of hemodialysis for treatment of overdose with XELJANZ/ XELJANZ XR.

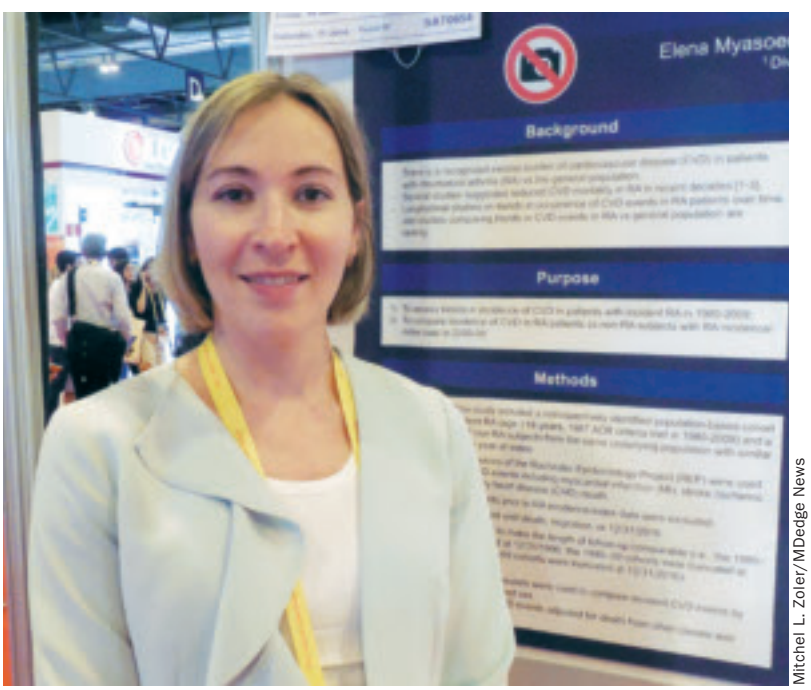
This brief summary is based on XELJANZ®/XELJANZ® XR (tofacitinib) Prescribing Information LAB-0445-18.0 Issued: August 2019

Cardiovascular events in U.S. rheumatoid arthritis patients fall to non–rheumatoid arthritis level

BY MITCHEL L. ZOLER
REPORTING FROM EULAR 2019 CONGRESS

MADRID – U.S. patients with rheumatoid arthritis stopped having an excess of cardiovascular disease events during the 2000s.

During both the 1980s and 1990s, patients with rheumatoid arthritis residing in a 27-county region in southeastern Minnesota and northwestern Wisconsin had cardiovascular disease event rates that were more than twice the rates in similar adults without RA, but that changed during the 2000s, Elena Myasoedova, MD, said in a poster she presented at the European Congress of Rheumatology. During 2000-2009, RA patients enrolled in the Rochester (Minn.) Epidemiology Project had an incidence of cardiovascular disease events at a rate that was 12% lower, compared with matched adults without RA who were also enrolled in the same regional database, reported Dr. Myasoedova, a rheumatologist at the Mayo Clinic in Rochester, and her associates.



Mitchel L. Zoler/MDedge News
Dr. Elena Myasoedova: The findings "give us a hint that tight control of RA disease activity is also likely to help cardiovascular disease burden."

"We hypothesize that improved management of RA, including implementation of a treat-to-target strategy and the introduction of biological drugs could have influenced this, as well as increased awareness of and improved prevention of cardiovascular disease," Dr. Myasoedova said in an interview. The findings "give us a hint that tight control of RA disease activity is also likely to help cardiovascular disease burden."

She and her associates identified 906 people enrolled in the Rochester Epidemiology Project who had incident RA based on the 1987 criteria of the American College of Rheumatology and matched them by age, sex, and index year with 905 people in the registry without RA. These cohorts included roughly 200 people from each subgroup tracked during the 1980s, 300 from each subgroup tracked during the 1990s, and about 400 in each subgroup tracked during the 2000s. They averaged about 56 years old, and about two-thirds were women.

During the 1980s, the cumulative incidence of nonfatal MI, nonfatal stroke, or cardiovascular disease (CVD) death was 2.11-fold more common among the RA patients than in the matched controls without RA, and during the 1990s this ratio showed a 2.13-fold excess of CVD events among the RA patients. The between-group differences in both decades were statistically significant. During the 2000s, the RA patients actually had a nominally lower rate of CVD events, at 0.88 times the rate of the controls, a difference that was not statistically significant.

Dr. Myasoedova and her associates had previously reported a similar finding in an analysis that used a smaller number of people and focused exclusively on rates of CVD (J Rheumatol. 2017 Jun;44[6]:732-9).

A few factors limit the generalizability of the finding, Dr. Myasoedova cautioned. First, the population studied was about 90% white. Also, people in the Rochester Epidemiology Project receive their medical care from clinicians at the Mayo Clinic or an affiliated hospital in the region covered by the Project.

"These data are from a large, tertiary care center," and so the findings are most directly applicable to patients who receive medical care in a similar setting that provides guideline-directed management of both RA and CVD risk.

A long-standing hypothesis is that CVD has an inflammatory component. These data support that concept by suggesting that, when inflammatory disease is well controlled in RA patients, their CVD risk drops, Dr. Myasoedova said. "CVD has been seen as the number one comorbidity for RA patients, and it remains that way, but it's very reassuring that the CVD rate has improved. It shows we're doing something right."

The study received no commercial funding. Dr. Myasoedova had no relevant disclosures.

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SOURCE: Myasoedova E et al. Ann Rheum Dis. Jun 2019;78(Suppl 2):1024-5, Abstract FRI0654. doi: 10.1136/annrheumdis-2019-eular.4996.

Corticosteroid use in pregnancy linked to preterm birth

BY BIANCA NOGRADY
FROM RHEUMATOLOGY

Pregnant women taking oral corticosteroids for rheumatoid arthritis may be at increased risk of preterm birth, according to research published online Sept. 30 in Rheumatology.

A study of 528 pregnant women with rheumatoid arthritis enrolled in the MotherToBaby Pregnancy Studies found that those taking a daily dose of 10 mg or more of prednisone equivalent – representing a mean cumulative dose of 2,208.6 mg over the first 139 days of pregnancy – had 4.77-fold higher odds of preterm birth, compared with those not taking oral corticosteroids. Women on medium doses – with a mean cumulative dose of 883 mg – had 81% higher odds of preterm birth, while those on low cumulative doses of 264.9 mg showed a nonsignificant 38% increase in preterm birth risk.

> The study did not find any effect of biologic or nonbiologic disease-modifying antirheumatic drugs.

Women who did not use oral corticosteroids before day 140 of pregnancy had a 2.2% risk of early preterm birth. Among women with low use of oral corticosteroids, the risk was 3.4%, among those with medium use the risk was 3.3%, but among those with high use the risk was 26.7%.

After day 140 of gestation, there was a nonsignificant 64% increase in the risk for preterm birth with any use of oral corticosteroids, compared with no use. But among women taking 10 mg or more of prednisone equivalent per day, the risk was 2.45-fold higher, whereas those taking under 10 mg showed no significant increase in risk.

"Systemic corticosteroid use has been associated with serious infection in pregnant women and serious and nonserious infection in individuals with autoimmune diseases, independent of other immunosuppressive medications, especially for doses of 10 mg of prednisone equivalent per day and greater," wrote Kristin Palmsten, ScD, a research investigator with HealthPartners Institute in Minneapolis, and coauthors.

Given that intrauterine infection is believed to contribute to preterm birth, some have suggested that the immunosuppressive effects of oral corticosteroids could be associated with an increased risk of preterm birth because of subclinical intra-amniotic infection, they wrote.

However, they noted that there was a lack of information on the effect of dose and timing of oral corticosteroids during pregnancy on the risk of preterm birth.

The authors acknowledged that dosage of oral corticosteroids during pregnancy was linked to disease activity, which was itself associated with preterm birth risk. They adjusted for self-assessed rheumatoid arthritis severity at enrollment, which was generally during the first trimester, and found that this did attenuate the association with preterm birth.

"Ideally, we would have measures of disease severity at the time of every medication start, stop, or dose change to account for time-varying confounding later in pregnancy," they wrote.

The study did not find any effect of biologic or nonbiologic disease-modifying antirheumatic drugs, either before or after the first 140 days of gestation.

The authors also looked at pregnancy outcomes among women with inflammatory bowel disease and asthma who were taking corticosteroids for those conditions.

Antonio_Diaz/Thinkstock

While noting that these estimates were "imprecise," they did see the suggestion of an increase in preterm birth among women taking oral corticosteroids for asthma, especially when used in the first half of pregnancy. There was also a suggestion of increased preterm birth risk associated with high oral corticosteroid use for inflammatory bowel disease, but these estimates were unadjusted, they noted.

"Overall, IBD and asthma exploratory analyses align with the direction of the associations in the RA analysis despite limitations of precision and inability to adjust for IBD severity," they wrote.

The conclusions to be drawn from the study are limited by its small size, the investigators noted, as well as a lack of information on the type of rheumatoid arthritis and longitudinal disease severity. They added that, while the hypothesized mechanism of action linking oral corticosteroid use to preterm birth was subclinical intrauterine infection, they did not have access to placental pathology to confirm this.

The study was supported by the National Institutes of Health, and the MotherToBaby Pregnancy Studies are supported by research grants from a number of pharmaceutical companies. No other conflicts of interest were declared.

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SOURCE: Palmsten K et al. Rheumatology. 2019 Sep 30. doi: 10.1093/rheumatology/kez405.

Prepare for deluge of JAK inhibitors for RA

BY BRUCE JANCIN
REPORTING FROM RWCS 2019


Bruce Jancin/MDedge News

Dr. Roy M. Fleischmann (left), with Dr. Mark Genovese: If the cost proves comparable, it makes sense to turn to a JAK inhibitor ahead of a tumor necrosis factor inhibitor or other biologic.

MAUI, HAWAII – As it grows increasingly likely that oral Janus kinase inhibitors will constitute a major development in the treatment of rheumatoid arthritis, with a bevy of these agents becoming available for that indication, rheumatologists are asking questions about the coming revolution. Like, when should these agents be used? What are the major safety and efficacy differences, if any, within the class? How clinically relevant is JAK selectivity? And which JAK inhibitor is the best choice?

Two experts with vast experience in running major randomized trials of the Janus kinase (JAK) inhibitors and other agents in patients with RA shared their views on these and other related questions at the 2019 Rheumatology Winter Clinical Symposium.

These issues take on growing relevance for clinicians and their RA patients because two oral small-molecule JAK inhibitors – tofacitinib (Xeljanz) and baricitinib (Olumiant) – are already approved for RA, and three more – upadacitinib, filgotinib, and peficitinib – are on the horizon. (**Editor's note:** Upadacitinib was approved under the brand name Rinvoq in August 2019.) Filgotinib is the focus of three phase 3 studies, one of which is viewed as a home run, with the other two yet to report results. Peficitinib is backed by two positive phase 3 trials, although its manufacturer will at least initially seek marketing approval only in Japan and South Korea. And numerous other JAK inhibitors are in development for a variety of indications.

When should a JAK inhibitor be used?

That's easy, according to Roy M. Fleischmann, MD: If the cost proves comparable, it makes sense to turn to a JAK inhibitor ahead of a tumor necrosis factor (TNF) inhibitor or other biologic.

He noted that, in the double-blind, phase 3 SELECT-COMPARE head-to-head comparison of upadacitinib at 15 mg/day, adalimumab (Humira) at 40 mg every other week, versus placebo, all on top of background methotrexate, upadacitinib proved superior to the market-leading TNF inhibitor in terms of both the American College of Rheumatology–defined 20% level of response (ACR 20) and 28-joint Disease Activity Score based on C-reactive protein (DAS28-CRP).

"The results were very dramatic," noted Dr. Fleischmann, who presented the SELECT-COMPARE findings at the 2018 annual meeting of the American College of Rheumatology.

Moreover, other major trials have shown that baricitinib at 4 mg/day was superior in efficacy to adalimumab, and tofacitinib and peficitinib were "at least equal" to anti-TNF therapy, he added.

"These numbers are clinically meaningful – not so much for the difference in ACR 20, but in the depth of response: the ACR 50 and 70, the CDAI [Clinical Disease Activity Index]. I think these drugs are better than adalimumab," declared Dr. Fleischmann, codirector of the division of rheumatology at Texas Health Presbyterian Medical Center, Dallas.

Mark Genovese, MD, concurred.

"I think that, for most patients who don't have a lot of other comorbidities, they would certainly prefer to take a pill over a shot. And if you have a drug that's more effective than the standard of care and it comes at a reasonable price point – and 'reasonable' is in the eye of the beholder – but if I can get access to it on the formulary, I'd have no qualms about putting them on a JAK inhibitor before I'd move to a TNF inhibitor," said Dr. Genovese, professor of medicine and director of the rheumatology clinic at Stanford (Calif.) University.

Upadacitinib elicited a better response at 30 mg than at 15 mg once daily in the phase 3 program; however, both speakers indicated they'd be happy with access to the 15-mg dose, should the FDA go that route, since it has a better safety profile.

Dr. Genovese was principal investigator in the previously reported multicenter FINCH2 trial of filgotinib at 100 or 200 mg/day in RA patients with a prior inadequate response to one or more biologic disease-modifying antirheumatic drugs.

"Impressive results in a refractory population," he said. "I don't see a big difference in safety between 100 and 200 mg, so I'd opt for the 200 because it worked really well in patients who had refractory disease."

Other advantages of JAK inhibitors

Speed of onset is another advantage in addition to oral administration and efficacy greater than or equivalent to

Continued on following page ▸

U.S. increases in RA burden beat global averages

BY RICHARD FRANKI
FROM ANNALS OF THE RHEUMATIC DISEASES

Three major indicators of rheumatoid arthritis burden in the United States all increased more rapidly than did global averages from 1990 to 2017, according to a new analysis of RA activity in 195 countries.

Percentage changes in the incidence, prevalence, and disability-adjusted life-year (DALY) rates for RA all reached double digits in the United States over the study period, but global increases for those measures stayed in the single digits, except for DALY, which did not increase, Saeid Safiri, PhD, of Tabriz (Iran) University of Medical Sciences and associates wrote in Annals of the Rheumatic Diseases.

Data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 show that RA incidence in the United States had the largest increase (20.7%) among the three measures, rising from 19.3 cases per 100,000 population in 1990 to 23.4 in 2017. Overall incidence for the 195 countries included in the study went from 13.7 to 14.9 cases per 100,000, for an increase of 8.2%, the investigators reported.

That pattern largely repeats for prevalence: an increase of 17.5% in the United States as the number of cases went from 336.5 per 100,000 in 1990 to 395.5 in 2017, and an increase of 7.4% globally, with the number of prevalent cases rising from 229.6 to 246.5 per 100,000, they said.

The DALY numbers – think of each DALY as 1 lost year of "healthy" life, the World Health Organization says – tell a somewhat different story. The United States had DALY rate of 53.2 per 100,000 in 1990, but by 2017 it had climbed to 60 per 100,000, an increase of 12.8%. Over that same time period, the global rate fell by 3.6% as it went from 44.9 to 43.3, Dr. Safiri and associates reported.

That long-term decline does, however, disguise a more recent trend. The global DALY rate "decreased from 1990 to 2012 but then increased and reached higher than expected levels in the following 5 years to 2017," they wrote.

RA rates in the United States in 2017 were, as noted, above average, but they were not the highest. The United Kingdom achieved the RA trifecta of highest incidence (27.5 per 100,000), highest prevalence (471.8 per 100,000), and highest DALY rate (73 per 100,000) among the 195 countries in the study. At the other end of the three scales, Indonesia had the lowest incidence (5.6 per 100,000) and prevalence (91.1 per 100,000), and Sri Lanka had the lowest DALY rate (14.2 per 100,000), they said.

"Age-standardized prevalence and incidence rates are overall increasing globally. Increasing population awareness regarding RA, its risk factors and the importance of early diagnosis and treatment with disease-modifying agents is warranted to reduce the future burden of this condition," the research team concluded.

GBD is funded by the Bill and Melinda Gates Foundation. The current analysis also was supported by Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences in Tehran, Iran. The investigators did not declare any conflicts of interest.

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SOURCE: Safiri S et al. Ann Rheum Dis. 2019 Sep 11. doi: 10.1136/annrheumdis-2019-215920.

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anti-TNF therapy, according to Dr. Genovese.

"As a class, JAK inhibitors have a faster onset than methotrexate in terms of improvement in disease activity and pain. So in a few weeks you can have a sense of whether folks are going to be responders," the rheumatologist said.

Does JAK isoform selectivity really make a difference in terms of efficacy and safety?

It's doubtful, the rheumatologists agreed. All of these oral small molecules target JAK1, and that's what's key.

Tofacitinib is relatively selective for JAK1 and JAK3, baricitinib for JAK1 and JAK2, upadacitinib and fibotinib for JAK1, and peficitinib is a pan-JAK inhibitor.

What are the safety concerns with this class of medications?

The risk of herpes zoster is higher than with TNF inhibitors, reinforcing the importance of varicella vaccination in JAK inhibitor candidates. Anemia occurs in a small percentage of patients. As for the risk of venous thromboembolism as a potential side effect of JAK inhibitors, a topic of great concern to the FDA, Dr. Fleischmann dismissed it as vastly overblown. "I think VTEs are an RA effect. You see it with all the drugs, including methotrexate," he said.

Idiosyncratic self-limited increases in creatine kinase have been seen in 2%-4% of patients on JAK inhibitors in pretty much all of the clinical trials. "I'm not aware of any cases of myositis, though," Dr. Fleischmann noted.

As for the teratogenicity potential of JAK inhibitors, Dr. Genovese said that, as is true for most medications, it hasn't been well studied.

Which JAK inhibitor is the best choice for treatment of RA?

It's impossible to say because of the hazards in trying to draw meaningful conclusions from cross-study comparisons, the experts agreed.

"It's a challenge. I think at the end of the day there will probably be one agent that looks like it might be best in class predicated on having the most number of indications, and that will probably become a preferred agent. The question is, does that happen before tofacitinib goes generic? And I don't know the answer to that," Dr. Genovese said.

Both rheumatologists disclosed financial relationships with more than a dozen pharmaceutical companies.

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Recognize and assess RA-related fatigue routinely, experts urge

BY SARA FREEMAN
REPORTING FROM EULAR 2019 CONGRESS

MADRID – Fatigue is one of the most frequent features of rheumatoid arthritis, and it needs to be assessed and addressed, several leading rheumatology experts urged at the European Congress of Rheumatology.

"Fatigue is an outcome of outstanding importance for patients with rheumatoid arthritis, and therefore it should be an outcome of outstanding importance for clinicians who take care of these patients," said José António Pereira da Silva, MD, PhD, a professor of rheumatology at the University of Coimbra (Portugal) during a clinical science session dedicated to the topic.

"Fatigue is described as being significant by as many as 40%-80% of all patients with rheumatoid arthritis, and described as being severe by 41%-49% of these patients according to different studies," Dr. da Silva said.

"The impact upon the quality of life from the patients' perspective is quite varied but always rather important, if not 'dramatic,'" Dr. da Silva said. Fatigue needs to be part of treatment targets alongside disease activity and thus regularly measured, he added.

Photos Sara Freeman/MDedge News

Dr. José António Pereira da Silva: Fatigue needs to be part of treatment targets alongside disease activity and regularly measured.

Dr. James Galloway: "Fatigue is … not just how well you sleep, but how much energy you have, and it's also how motivated you are."

The problem of fatigue

The problem, however, is that fatigue is such a complex construct, observed James Galloway, MBChB, PhD, of the Centre for Rheumatic Diseases at King's College London. "It's definitely multifactorial in origin; it's a combination of inflammatory disease, psychosocial situations, and comorbidity."

Moreover, said Dr. Galloway, "what people describe as fatigue is multidimensional; it's not just how well you sleep, but how much energy you have, and it's also how motivated you are." The fatigue that accompanies RA is different from the fatigue that is experienced in daily life, he noted, and it has a huge impact on patients' lives.

Determining the cause of fatigue can be challenging, said Wan-Fai Ng, MBChB, PhD, professor of rheumatology at the Institute of Cellular Medicine at Newcastle (England) University.

"Fatigue is a syndrome that often coexists with other symptoms, and there may be different types of fatigue," Dr. Ng said. He noted that there were many potential underlying biological mechanisms, but the most studied so far is inflammation. Fatigue is probably driven, at least in part, by "sickness behavior" and there are frequent associations between fatigue and chronic inflammatory conditions such as RA and Sjögren's syndrome.

"I think the role of conventional inflammatory mechanisms, at least in chronic fatigue in chronic conditions, remains unclear," Dr. Ng added. "The biological systems, for example the vagus nerve, that regulate the immune system may play key roles in fatigue, especially in chronic inflammatory states."

Whatever the underlying mechanism, it's clear that there are multiple factors at play that need addressing if fatigue is to be properly addressed in the clinic. Dr. da Silva unveiled a new path analysis model that will be published in a future issue of Clinical and Experimental Rheumatology that showed how disease activity, pain, disability, sleep disturbance, and depression might all interlink to account for fatigue in patients with RA.

How should fatigue in RA be assessed?

"Fatigue is recognized by OMERACT [Outcome Measures in Rheumatology Clinical Trials group] as being one of the measured outcome factors in rheumatoid arthritis, one that we should all be taking care of," Dr. da Silva said. It was added alongside the core set of measures that should be used in all trials "wherever possible."

So how should fatigue be measured in practice? There are lots of instruments available. Indeed, Dr. da Silva and associates recently counted more than 12, but there is no consensus and no guidelines on which should be used.

"We propose to use a single-item instrument as a screening tool, like the BRAF NRS [Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale] or RAID-F [Rheumatoid Arthritis Impact of Disease–Fatigue domain], which would be supplemented by additional multidimensional assessments if significant levels of fatigue are identified," he said in an interview. "This will be particularly useful when the

Continued on following page ▸

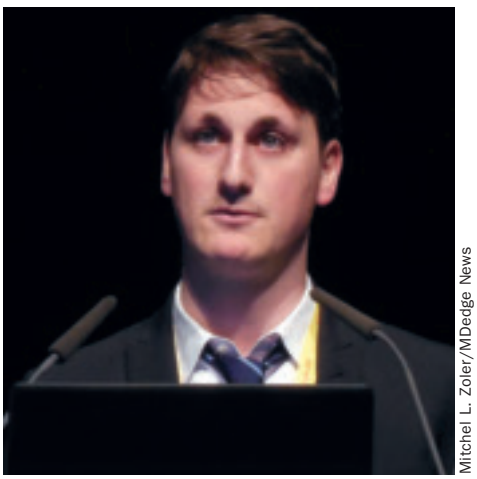
Flu vaccine succeeds in TNF inhibitor users

BY HEIDI SPLETE
REPORTING FROM EULAR 2019 CONGRESS

MADRID – Influenza vaccination is similarly effective for individuals taking a tumor necrosis factor (TNF) inhibitor and healthy controls, but the number needed to vaccinate to prevent one case of influenza for patients taking a TNF inhibitor is much lower, according to data from a study presented at the European Congress of Rheumatology.

The number needed to vaccinate (NNV) to prevent one case of influenza among healthy control patients was 71, compared with an NNV of 10 for patients taking the TNF inhibitor adalimumab (Humira), reported Giovanni Adami, MD, and colleagues at the University of Verona (Italy).

While TNF inhibitors "are known to increase the risk of infection by suppressing the activity of the immune system," it has not been clear whether the response to vaccination is impaired in patients treated with a TNF inhibitor, Dr. Adami said.



Mitchel L. Zoler/MDedge News

Dr. Giovanni Adami: The number needed to vaccinate to prevent one case of influenza among healthy control patients was 71, compared with a NNV of 10 for patients taking adalimumab.

Dr. Adami and colleagues reviewed data from 15,132 adult patients exposed to adalimumab in global rheumatoid arthritis clinical trials and 71,221 healthy controls from clinical trials of influenza vaccines. Overall, the rate of influenza infection was similarly reduced with vaccination in both groups. The rate in healthy individuals went from 2.3% for those unvaccinated to 0.9% for those vaccinated; for TNF inhibitor–treated patients, the rate was 14.4% for those unvaccinated versus 4.5% for those vaccinated.

"It is not surprising that the number needed to vaccinate is dramatically lower in patients treated with immunosuppressors, compared to healthy individuals," he noted. "As a matter of fact, patients treated with such drugs are at higher risk of infections, namely they have a greater absolute risk of influenza. Nevertheless, [it] is quite surprising that the relative

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aims are to explore causality of fatigue or the efficacy of an intervention."

Dr. da Silva noted after his presentation that the RAID-F score is routinely used at his practice. "It's an extremely useful instrument in trying to assess how the patient is dealing with rheumatoid arthritis," he said. He emphasized that fatigue needed to be considered separately from disease activity and that "it should be part of treatment targets and it should be regularly measured in both research and clinical practice."

How can fatigue in RA be treated?

When faced with a patient with RA who is experiencing fatigue, it's important to take a full history and try to determine the cause or contributing factors, Dr. Galloway advised. "I think it's really important to [take a history of this] specific symptom in the same way you take a history of articular pain." Consider the onset of fatigue, for example. Is it sudden or linked to a particular stressor or life event, or has its development been more gradual? What's been the clinical course, duration, and daily pattern? Are there any factors that might alleviate it or exacerbate it? What's the impact on the patient's daily life – both in terms of work and social participation?

Treating RA more effectively might help, "but that is unlikely to be sufficient," Dr. Galloway said, observing that "leaving uncontrolled inflammation is bad, but, in 2019, more inflammation is probably not the solution to fatigue." Instead, he suggested looking for and treating comorbidities that might be contributing to the fatigue, such as anemia, endocrine or cardiac disease, or perhaps sleep apnea or depression, among others.

"I would discourage the prescribing, for the large part, of drugs for fatigue; that's because that's where the evidence is probably the least strong," Dr. Galloway said. However, there is much better evidence for the use of exercise training in RA and for combining exercise and psychosocial approaches. Improving sleep hygiene may also be beneficial for some patients.

The bottom line is that "fatigue matters" and should be "talked about more with our patients," Dr. Galloway said.

Dr. da Silva had no financial conflicts of interest. Dr. Ng disclosed research collaborations with Resolve Therapeutics, electroCore, GlaxoSmithKline, and AbbVie. He also disclosed acting as a consultant for Novartis, GlaxoSmithKline, AbbVie, MedImmune, Pfizer, and Bristol-Myers Squibb. Dr. Galloway disclosed receiving honoraria for speaking at meetings, support for conference travel, or both from AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Pfizer, and UCB.

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SOURCES: da Silva JAP. Ann Rheum Dis. Jun 2019;78(Suppl 2):15, Abstract SP0052. doi: 10.1136/annrheumdis-2019-eular.8454; Galloway J. Ann Rheum Dis. Jun 2019;78(Suppl 2):15, Abstract SP0053. doi: 10.1136/annrheumdis-2019-eular.8483; Arnstad ED et al. Ann Rheum Dis. Jun 2019;78(Suppl 2):176, Abstract OP201. doi: 10.1136/annrheumdis-2019-eular.4006.

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

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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.

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[a]Studied in adult patients with moderate to severe RA. [b]SELECT-EARLY (RA-I; MTX-naïve) [primary endpoint at Week 12: ACR50 response vs MTX, select ranked secondary endpoint at Week 24: ΔmTSS vs MTX]; SELECT-MONOTHERAPY (RA-II; MTX-IR) [primary endpoint at Week 14: ACR20 response vs MTX, select ranked secondary endpoint at Week 14: DAS28-CRP<2.6 vs MTX]; SELECT-NEXT (RA-III; csDMARD-IR) [RINVOQ + csDMARD; primary endpoint at Week 12: ACR20 response vs placebo + csDMARD, select ranked secondary endpoint at Week 12: DAS28-CRP<2.6 vs placebo + csDMARD]; SELECT-COMPARE (RA-IV; MTX-IR) [RINVOQ + MTX; primary endpoint at Week 12: ACR20 response vs placebo + MTX, select ranked secondary endpoints at Week 12: DAS28-CRP<2.6 vs placebo + MTX, HAQ-DI vs placebo + MTX, ACR50 response vs a TNFi + MTX, HAQ-DI vs a TNFi + MTX, pain reduction vs a TNFi + MTX; ΔmTSS vs placebo + MTX at Week 26]; SELECT-BEYOND (RA-V; bDMARD-IR) [RINVOQ + csDMARD; primary endpoint at Week 12: ACR20 response vs placebo + csDMARD]. [c]RINVOQ 15 mg; upadacitinib 30 mg; methotrexate; TNFi, placebo. [d]Long-term data as of 11/14/18.

ACR=American College of Rheumatology; bDMARD-IR=inadequate response or intolerance to biologic disease-modifying antirheumatic drug; csDMARD=conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR=inadequate response or intolerance to conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score 28 joints, c-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; JAK=Janus kinase; mTSS=modified total Sharp score; MTX=methotrexate; MTX-IR=inadequate response or intolerance to methotrexate; TNFi=tumor necrosis factor inhibitor.

MALIGNANCY

Lymphoma and other malignancies have been observed in RINVOQ-treated patients.

THROMBOSIS

Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions.

OTHER SERIOUS ADVERSE REACTIONS

Patients treated with RINVOQ also may be at risk for other serious adverse reactions, including gastrointestinal perforations, neutropenia, lymphopenia, anemia, lipid elevations, liver enzyme elevations, and embryo-fetal toxicity.

Please see additional Important Safety Information, including BOXED WARNING on Serious Infections, Malignancy, and Thrombosis, on the following page of this advertisement.

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RINVOQ™
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IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent 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.

MALIGNANCY

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. Consider the risks and benefits of treatment with RINVOQ prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or in patients who develop a malignancy. NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. Consider the risks and benefits prior to treating patients who may be at increased risk. Patients with symptoms of thrombosis should be promptly evaluated.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in clinical studies with RINVOQ, although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with nonsteroidal anti-inflammatory drugs (NSAIDs). RINVOQ should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal 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 clinical studies. 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 clinical studies. Treatment should not be initiated or should be interrupted in patients with hemoglobin levels <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

Lipids

Treatment with RINVOQ was associated with 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 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 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

Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, patients should be brought up to date on all immunizations, including prophylactic 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 in patients with severe hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions in RINVOQ clinical trials (≥1%) were: upper respiratory tract infection, nausea, cough, and pyrexia.

References: 1. RINVOQ [package insert]. North Chicago, IL: AbbVie Inc; 2019. **2.** Data on file, AbbVie Inc. ABVRRTI68885. **3.** Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase 3, double-blind, randomized controlled trial [published online July 9, 2019]. *Arthritis Rheumatol.* doi:10.1002/art.41032 **4.** Supplement to: Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase 3, double-blind, randomized controlled trial [published online July 9, 2019]. *Arthritis Rheumatol.* doi:10.1002/art.41032 **5.** Cohen SB, van Vollenhoven R, Winthrop K, et al. Safety Profile of Upadacitinib in Rheumatoid Arthritis: Integrated Analysis From the SELECT Phase 3 Clinical Program. Presented at: EULAR Annual Meeting; June 12–15, 2019; Madrid, Spain. **6.** Data on file, AbbVie Inc. ABVRRTI68550.

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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]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ *[see Warnings and Precautions]*.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. Consider the risks and benefits prior to treating patients who may be at increased risk. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

RINVOQ™ (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

Limitation 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

None

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

Patients should be screened for tuberculosis (TB) before starting RINVOQ therapy. RINVOQ should not be given to patients with active TB. Anti-TB therapy should be considered 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.

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 studies with RINVOQ *[see Adverse Reactions]*. 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 studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 studies of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

Malignancy

Malignancies were observed in clinical studies of RINVOQ *[see Adverse Reactions]*. Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing RINVOQ in patients who develop a malignancy.

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.

Thrombosis

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

Consider the risks and benefits of RINVOQ treatment prior to treating patients who may be at increased risk of thrombosis. If symptoms of thrombosis occur, patients should be evaluated promptly and treated appropriately.

Gastrointestinal Perforations

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

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

Laboratory Parameters

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

Lymphopenia

ALC less than 500 cells/mm^3 were reported in RINVOQ clinical studies.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid initiation of 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 clinical studies.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid initiation of 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.

Patients should be monitored 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 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 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. 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 following completion of therapy *[see Use in Specific Populations]*.

Vaccination

Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, including prophylactic 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]*
- Malignancy *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Gastrointestinal Perforations *[see Warnings and Precautions]*
- Laboratory Parameters *[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.

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the Phase 3 clinical studies 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 study 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 studies 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 2: Adverse Reactions Reported in greater than or equal to 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Studies

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 Studies: Studies 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). Studies RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), upadacitinib 30 mg (n=384). Study 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 studies RA-III and RA-V.

MTX-controlled Studies: Studies 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: Studies 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 study for all the adverse events reported in this section.

Specific Adverse Reactions

Infections

Placebo-controlled Studies: 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 Studies: 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 Studies: 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 Studies: 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 Studies and MTX-controlled Studies: 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 Studies: 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 Studies: 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.

Malignancy

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

MTX-controlled Studies: 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 Studies: 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 Studies: 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 studies (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 studies, 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 studies, 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 studies (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 studies (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 studies, treatment was interrupted in response to ANC less than 500 cells/mm^3.

Lymphopenia

In placebo-controlled studies (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 studies (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.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole). RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors.

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when 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

The limited human data 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, upadacitinib has the potential to adversely affect a developing 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 maximum recommended human dose (MRHD), respectively, 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 approximately 0.3 and 2 times the exposure at the MRHD. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the MRHD resulted in no maternal or developmental toxicity *[see Animal Data]*.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. 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 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 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 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 0.3 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 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 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 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. 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 upadacitinib, and for 6 days (approximately 10 half-lives) after the last dose.

Data

Animal Data

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Pediatric Use

The safety and efficacy of RINVOQ in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Geriatric Use

Of the 4381 patients treated in the five Phase 3 clinical studies, a total of 906 rheumatoid arthritis patients were 65 years of age or older, including 146 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 in the elderly.

Renal Impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment. The use of RINVOQ has not been studied in subjects with end stage renal disease.

Hepatic Impairment

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. RINVOQ is not recommended for use in patients with severe hepatic impairment (Child Pugh C).

OVERDOSAGE

Upadacitinib was administered in clinical trials up to doses equivalent in daily AUC to 60 mg extended-release once daily. Adverse events were comparable to those seen at lower doses and no specific toxicities were identified. Approximately 90% of upadacitinib in the systemic circulation is eliminated within 24 hours of dosing (within the range of doses evaluated in clinical studies). In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the MRHD on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negatively in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 42 and 84 times the MRHD in males and females, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 22 and 84 times the MRHD on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 2 times the MRHD on an AUC basis).

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. Instruct patients to inform their healthcare provider if they have ever had any type of cancer *[see Warnings and Precautions]*.

Thrombosis

Advise patients that events of DVT and PE have been reported in clinical studies with RINVOQ. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions]*.

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]*.

Pregnancy

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]*.

Lactation

Advise women not to breastfeed during treatment with RINVOQ *[see Use in Specific Populations]*.

Administration

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

Manufactured by: AbbVie Ireland NL B.V., Sligo, Ireland
Packed and Distributed by: AbbVie Inc., North Chicago, IL 60064

Ref: 03-B725 Revised: August, 2019
LAB-2721 **MASTER**

US-RNQR-190403

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Flu shot can be given irrespective of the time of last methotrexate dose

BY NICOLA GARRETT
FROM ANNALS OF THE RHEUMATIC DISEASES

Immune response to influenza vaccination in rheumatoid arthritis patients taking methotrexate appears to depend most on stopping the next two weekly doses of the drug rather than any effect from the timing of the last dose, new research concludes.

The new finding, reported in Annals of the Rheumatic Diseases, stems from a post hoc analysis of a randomized, controlled trial that Jin Kyun Park, MD, of Seoul (Korea) National University, and his colleagues had conducted earlier on immune response when patients stopped methotrexate for either 2 or 4 weeks after vaccination. While the main endpoint of that study showed no difference in the improvement in vaccine response with either stopping methotrexate for 2 or 4 weeks and no increase in disease activity with stopping for 2 weeks, it was unclear whether the timing of the last dose mattered when stopping for 2 weeks.

In a bid to identify the optimal time between the last dose of methotrexate and administration of a flu vaccine, Dr. Park and his colleagues conducted a post hoc analysis of the trial, which involved 316 patients with RA receiving methotrexate for 6 weeks or longer to continue (n = 156) or to hold (n = 160) methotrexate for 2 weeks after receiving a quadrivalent influenza vaccine containing H1N1, H3N2, B-Yamagata, and B-Victoria.

The study authors defined a positive vaccine response as a fourfold or greater increase in hemagglutination inhibition (HI) antibody titer. A satisfactory vaccine response was a positive response to two or more of four vaccine antigens.

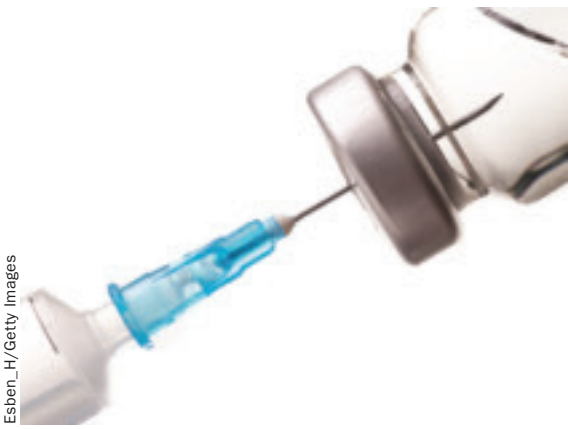
Patients who stopped taking methotrexate were divided into eight subgroups according to the number of days between their last dose and their vaccination.

The research team reported that response to vaccine, fold increase in HI antibody titers, and postvaccination seroprotection rates were not associated with the time between the last methotrexate dose and the time of vaccination.

However, they conceded that "the absence of impact of the number of days between the last methotrexate dose and vaccination could be due to the small patient numbers in eight subgroups."

Vaccine response also did not differ between patients who received the influenza vaccination within 3 days of the last methotrexate dose (n = 65) and those who received it in 4-7 days of the last methotrexate dose (n = 95).

Furthermore, RA disease activity, seropositivity, or use of conventional or biologic disease-modifying antirheumatic drugs did not have an impact on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methotrexate discontinuation.

The authors concluded that vaccinations could be given irrespective of the time of the last methotrexate dose, and patients should be advised to skip two weekly doses following vaccination.

"This supports the notion that the effects of methotrexate on humeral immunity occur rapidly, despite the delayed effects on arthritis; therefore, the absence of methotrexate during the first 2 weeks postvaccination is critical for humoral immunity," they wrote.

The study was sponsored by GC Pharma. One author disclosed serving as a consultant to Pfizer and receiving research grants from GC Pharma and Hanmi Pharma.

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SOURCE: Park JK et al. Ann Rheum Dis. 2019 Mar 23. doi: 10.1136/annrheumdis-2019-215187.

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risk reduction is similar between TNF inhibitor–treated patients and healthy controls, meaning that the vaccination is efficacious in both the cohorts."

The researchers also calculated the cost to prevent one case of influenza, using a cost of approximately 16.5 euro per vaccine. (Dr. Adami also cited an average U.S. cost of about $40/vaccine.) Using this method, they estimated a cost for vaccination of 1,174 euro (roughly $1,340) to prevent one influenza infection in the general population, and a cost of about 165 euro (roughly $188) to vaccinate enough people treated with a TNF inhibitor to prevent one infection.

Dr. Adami advised clinicians to remember the low NNV for TNF inhibitor–treated patients with regard to influenza vaccination. "A direct disclosure of the NNV for these patients might help adherence to vaccinations," he said.

Next steps for research should include extending the real-world effectiveness analysis to other medications and other diseases, such as zoster vaccination in patients treated with Janus kinase inhibitors, Dr. Adami said.

Dr. Adami had no financial conflicts to disclose. Several coauthors disclosed relationships with multiple companies.

Mitchel L. Zoler contributed to this report.

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SOURCE: Adami G et al. Ann Rheum Dis. Jun 2019;78(Suppl 2):192-3, Abstract OP0230. doi: 10.1136/annrheumdis-2019-eular.3088.

Methotrexate does not cause rheumatoid arthritis interstitial lung disease

BY SARA FREEMAN
REPORTING FROM BSR 2019

BIRMINGHAM, ENGLAND – Data from two early RA inception cohorts provide reassurance that methotrexate does not cause interstitial lung disease and suggest that treatment with methotrexate might even be protective.

In the Early RA Study (ERAS) and Early RA Network (ERAN), which together include 2,701 patients with RA, 101 (3.7%) had interstitial lung disease (ILD). There were 92 patients with RA-ILD who had information available on exposure to any conventional synthetic disease-modifying antirheumatic drug (csDMARD); of these, 39 (2.5%) had been exposed to methotrexate (n = 1,578) and 53 (4.8%) to other csDMARDs (n = 1,114).

Multivariate analysis showed that methotrexate exposure was associated with a reduced risk of developing ILD, with an odds ratio of 0.48 (P = .004). In a separate analysis that excluded 25 patients who had ILD before they received any csDMARD therapy (n = 67), there was no association between methotrexate use and ILD (OR, 0.85; P = .578). In fact, there was a nonsignificant trend for a delayed onset of ILD in patients who had been treated with methotrexate (OR, 0.54; P = .072).

Methotrexate use is associated with an acute hypersensitivity pneumonitis in patients with RA, explained Patrick Kiely, MBBS, PhD, of St. George's University Hospitals NHS Foundation Trust in London at the British Society for Rheumatology annual conference. "This is well recognized, it's very rare [0.43%-1.00%], it's easy to spot, and usually goes away if you stop methotrexate," said Dr. Kiely, adding that "it's not benign, and severe cases can be life threatening."

Because of the association between methotrexate and pneumonitis, there has been concern that methotrexate may exacerbate or even cause ILD in RA but there are sparse data available to confirm this. The bottom line is that you should not start someone on methotrexate if you think their existing lung capacity is not up to treatment with it, he said.

Sara Freeman/MDedge News

Dr. Patrick Kiely: "We found no association between methotrexate treatment and incident RA-ILD."

ILD is not always symptomatic in RA, but when it is, it is associated with very poor survival. The lung disease can be present before joint symptoms, Dr. Kiely said. Although less than 10% of cases may be symptomatic, this "is a big deal, because it has a high mortality, with death within 5 years. It's the second-commonest cause of excess mortality in RA after cardiovascular disease."

To look at the association between incident RA-ILD and the use of methotrexate, Dr. Kiely and associates analyzed data from ERAS (1986-2001) and ERAN (2002-2013), that together have more than 25 years of follow-up data on patients who were recruited at the first sign of RA symptoms. Patients within these cohorts have been treated according to best practice, and a range of outcomes – including RA-ILD – have been assessed at annual intervals.

In the patients who developed ILD after any csDMARD exposure, older age at RA onset (OR, 1.04; P less than .001) and having ever smoked (OR, 1.91; P = .016) were associated with the development of the lung disease. Incident ILD was also associated with being positive for rheumatoid factor (OR, 2.02; P = .029) at baseline. Being male was also associated with a higher risk for developing ILD, as was a longer duration of time between the onset of first RA symptoms and the first secondary care visit. Conversely, the presence of nonrespiratory, major comorbidities at baseline appeared to be protective (OR, 0.62; P = .027).

"We found no association between methotrexate treatment and incident RA-ILD and a possibility that it may be protective," Dr. Kiely concluded, noting that these data were now published in BMJ Open (2019;9:e028466. doi: 10.1136/bmjopen-2018-028466).

Following Dr. Kiely's presentation, an audience member asked if the protective effect seen with methotrexate could have been caused by better disease control overall.

Dr. Kiely answered that, up until 2001, the time when ERAS was ongoing, standard practice in the United Kingdom was to use sulfasalazine, but then methotrexate started to be used in higher and higher doses, as seen in ERAN.

The interesting thing is that in ERAN more methotrexate was used in higher doses, but less RA-ILD was seen, Dr. Kiely observed. The overall prevalence of RA-ILD in the later early RA cohort was 3.2% and the median dose of methotrexate used was 20 mg. In ERAS, the prevalence was 4.2% and the median dose of methotrexate used was 10 mg.

Disease control was slightly better in ERAN than ERAS, but that wasn't statistically significant, Dr. Kiely said.

So, should a patient with RA and ILD be given methotrexate? There's no reason not to, Dr. Kiely suggested, based on the evidence shown. Part of the challenge will now be convincing chest physician colleagues that methotrexate is not problematic in terms of causing ILD.

The study had no specific outside funding. Dr. Kiely reported having no conflicts of interest.

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SOURCE: Kiely P et al. Rheumatology. 2019;58(suppl 3), Abstract 009.

Efficacy in phase 2 trials often missing in phase 3

BY MITCHEL L. ZOLER
REPORTING FROM EULAR 2019 CONGRESS

MADRID – The efficacy results from new rheumatoid arthritis drugs tested in many phase 2 trials run over the past couple of decades have routinely overestimated the efficacy of many of the drugs tested when compared with how the same agents performed in subsequent phase 3 testing, according to an analysis of published results from 44 pairs of phase 2 and 3 trials.

Based on the percentage of rheumatoid arthritis patients who showed an American College of Rheumatology 20% improvement (ACR20) in their joint symptoms, the 44 phase 2 trials overestimated efficacy by an average of 39% when compared with the ACR20 responses seen in paired phase 3 trials, Andreas Kerschbaumer, MD, said at the European Congress of Rheumatology. The ACR50 results overstated efficacy by an average of 34% when compared with phase 3 results for the same drugs, and the ACR70 endpoint showed drug efficacy that averaged 39% better during phase 2 studies than it did in the phase 3 trials. All three between-group differences were statistically significant, said Dr. Kerschbaumer, a rheumatologist at the Medical University of Vienna.

Mitchel L. Zoler/MDedge News

Dr. Andreas Kerschbaumer: "Some people get very excited by phase 2 results, but we need to be careful about interpreting these outcomes."

"Active-treatment arms of phase 2 studies systematically overestimated efficacy when compared with subsequent phase 3 studies," he said.

"Many researchers had already seen this, and realized that phase 2 trials often overestimated [efficacy], but no one has ever shown this systematically," Dr. Kerschbaumer said in an interview. The same problem also appears to affect trials of oncology drugs, he noted, but a unique feature of RA studies allowed him and his colleagues to examine the ubiquity and persistence of this phase 2 bias in rheumatology trials over time: ongoing reliance during more than 2 decades of experience on the ACR20 response as the primary endpoint of RA drug trials. Even with this advantage, which allowed inclusion of 44 pairs of studies, "it was very surprising to find a statistically significant effect in the meta-analysis," he said.

He and his associates also ran a further analysis that looked for measured parameters that showed significant correlation with mismatch of the phase 2 and 3 results, and this identified two apparently causal factors: having a low number of swollen and tender joints as an inclusion criterion for patients and using a 28-joint count rather than a 66-joint count for assessing disease activity during the study. The analysis lacked enough information to provide clear evidence on why these two aspects of patient assessment could lead to misleading phase 2 results, but Dr. Kerschbaumer believed the findings were clear enough to influence future trial design.

Going forward, trialists "should be very careful of how you include patients [in studies]. This is what our study shows. And they should not use 28 joints but 66. The higher the number of swollen and tender joints detected for study inclusion, the less the possibility to overestimate [efficacy]. It's easier to achieve ACR20 when you look at fewer joints."

Until now, companies that sponsor drug trials had an incentive to use a lower minimum number of swollen and tender joints for enrolled patients because it made enrollment easier, he noted. The downside, in addition to overstating efficacy at the phase 2 stage, is subjecting patients to treatments in phase 3 trials with a reduced likelihood for success.

Dr. Kerschbaumer offered two examples of drugs that showed promising RA efficacy based on ACR20 responses in phase 2 trial results that were followed by neutral phase 3 trial outcomes. One episode involved tabalumab (Ann Rheum Dis. 2015 Aug;74[8]:1567-70), and a second was a trial of fostamatinib (Arthritis Rheumatol. 2014 Dec;66[12]:3255-64).

The systematic review he led identified 44 study pairs run since the late 1990s that met all the study criteria, which covered 19 different drugs tested in more than 17,000 RA patients.

What the results showed was "just an association, so we must be careful not to overstate the results, but we saw something that may explain what people have seen [anecdotally] over the past 20 years," he said. "Some people get very excited by phase 2 results, but we need to be careful about interpreting these outcomes." Validation of the finding would require analysis of patient-level data, something that would be hard to obtain for a large number of phase 2 and 3 trials, Dr. Kerschbaumer noted.

Dr. Kerschbaumer has been a speaker on behalf of Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, and Pfizer.

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SOURCE: Kerschbaumer A et al. Ann Rheum Dis. Jun 2019;78(Suppl 2):191-2, Abstract OP0229. doi: 10.1136/annrheumdis-2019-eular.5161.

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3–6 June 2020