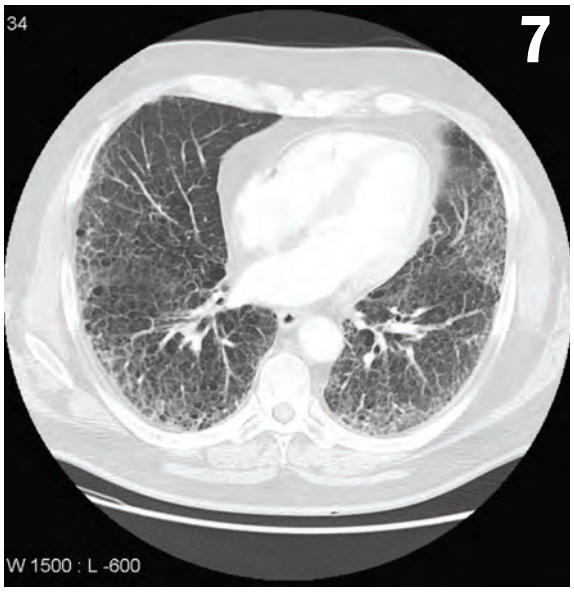
A SUPPLEMENT TO Rheumatology News

Best of 2018

The RA Report

Top News Highlights



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Treat to target in RA: Finding the right path forward

BY MICHELE G. SULLIVAN

It makes intuitive sense: Setting a specific goal and working quickly and systematically toward it should bring better results than slowly floundering toward an amorphous endpoint.

That's the basic idea behind treat-to-target (TTT) strategies in rheumatoid arthritis, and since 2010, data seem to support it: Rheumatologists who pick a therapeutic goal and a related disease activity measure, and work in partnership with cooperative patients to achieve it, get better clinical responses.

So important has this concept become that it's now being tied to reimbursement. Rheumatologists who submit proof that they record disease activity measures in their patients will get points toward fulfilling quality reporting requirements for the Merit-Based Incentive Payment System (MIPS) option in the Quality Payment Program established by the Medicare Access and CHIP Reauthorization Act of 2015. Those points go toward achieving a bonus in Medicare reimbursement; those who can't show it will edge toward a financial ding.

But despite the twin carrots of better patient outcomes and bonus payments from the Centers for Medicare & Medicaid Services and the stick of a 4%-9% Medicare payment penalty during the years 2019-2022 (and 9% thereafter) for quality outcome measures reported in 2017 and beyond, studies show that up to 60% of U.S. rheumatologists don't regularly incorporate TTT strategies into how they treat their RA patients.

Courtesy UAB Photo

Dr. Jeffrey Curtis: "I would say the No. 1 reason it's had limited adoption is that it simply hasn't been made easy enough."

"It's not an easy question, and there's not a single answer," said Jeffrey Curtis, MD, the William J. Koopman Professor of Rheumatology and Immunology at the University of Alabama, Birmingham.

"There are patient reasons. There are doctor reasons. And there are extrinsic reasons. But I would say the No. 1 reason it's had limited adoption is that it simply hasn't been made easy enough."

The ABCs of TTT

In 2010, Austrian rheumatologist Josef Smolen, MD, leading an international task force, proposed 10 recommendations for improving the care of patients with RA. These were based on the concept that choosing a therapeutic target – low disease activity or remission – and aggressively pursuing it with frequent medication changes accompanied by frequent disease activity measurements would result in improved short- and long-term outcomes.

Disease activity measures (DAMs) were crucial to the concept. In order to treat to a target, one must not only choose a target but also have a validated means to regularly measure progress. The task force didn't say which DAM would be most appropriate, and research since then suggests that the tool used to measure progress doesn't matter nearly as much as the target itself.

Shared decision making is also a core tenet of the technique. Physicians work with patients to identify the best treatment target for each individual and decide together how to reach it.

It is not a new concept, Dr. Smolen

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and his colleagues explained in their landmark paper (Ann Rheum Dis. 2010 Apr;69[4]:631-7). "In many other areas of medicine, treatment targets have been defined to improve outcomes, leading to a reduction in the risk of organ damage. In the care of patients with diabetes, hyperlipidemia, and hypertension, these aspects have been adopted widely in practice; doctors order laboratory tests for cholesterol and triglycerides, blood glucose and HbA_{1c} [hemoglobin A_{1c}] levels, check blood pressure, and adapt therapy accordingly, and patients know these values and are aware of the treatment targets."

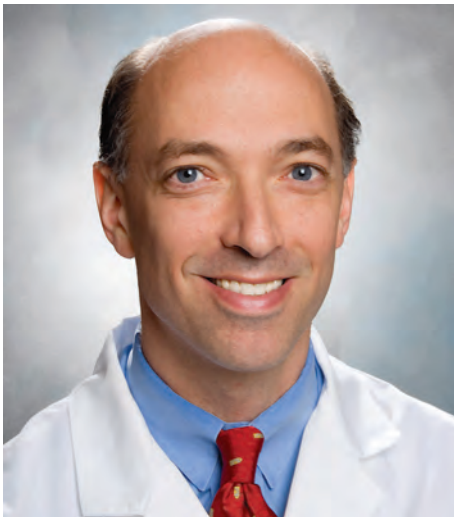
Yet rheumatologists had not adopted a similar paradigm, despite the surge in availability of effective disease-modifying antirheumatic drugs (DMARDs). Although clinical studies of these new drugs clearly showed that remission was possible for many patients and that achieving remission quickly could prevent irreversible joint damage, few patients were getting those drugs even if they had long-standing disease.

The task force suggested setting a treatment aim of remission or low disease activity, seeing patients every 1-3 months, and switching therapy as often as necessary to reach that goal. Tracking improvement required consistent measurements and recording of a DAM. The recommendations, which were updated in 2014, didn't specify a certain DAM, saying that the patient's individual clinical picture should guide that choice (Ann Rheum Dis. 2016 Jan;75[1]:3-15). Shared decision making between the patient and rheumatologist was at the foundation of this concept.

Fast-forward to 2015. As TTT was increasingly embraced in Europe, data began to emerge supporting its clinical validity. A study presented at the American College of Rheumatology (ACR) annual meeting in San Francisco that year showed that treating RA patients toward a target of remission or low disease activity worked immediately and resulted in higher remission rates.

Sofia Ramiro, MD, of Leiden (the Netherlands) University Medical Center found that employing a TTT strategy increased the likelihood that a patient would achieve remission by 52%. She also found that TTT strategies lowered disease activity and even improved remission rates for patients who had never received DMARDs.

But in 2017, a meta-analysis found



Dr. Daniel H. Solomon: Rheumatologists can implement TTT when given the right tools.

conflicting results among the 16 published randomized, controlled trials comparing TTT against usual care (Health Technol Assess 2017. doi: 10.3310/hta21710). The authors concluded that TTT was more effective for newly diagnosed patients, in whom it increased the chance of remission by about 50%. For those with longstanding disease, TTT was not significantly different from usual care.

Despite limited, and somewhat contradictory, clinical evidence, TTT is becoming increasingly accepted, especially in Europe. In 2016, the European League Against Rheumatism updated its recommendations for RA management (Ann Rheum Dis. 2017 Jun;76[6]:960-77). The document contained a recommendation to use low disease activity or sustained remission as the treatment target for every patient, to monitor disease activity with a validated measure every 1-3 months, and to change therapy as often as every 3 months in the case of no improvement or by 6 months if the target hasn't been reached.

In its most recent 2015 RA treatment guidelines, the ACR also endorsed the strategy, though somewhat obliquely, and did not require rheumatologists to conform to it (Arthritis Care Res. 2016 Jan;68[1]:1-25).

The concept of TTT, if not the explicit demand to practice it, now appears in the list of quality indicators rheumatologists can choose from in order to fulfill quality performance reporting requirements in Merit-Based Incentive Payment System. Periodic assessment of disease activity in RA patients with a validated DAM is one of the acceptable quality measures for rheumatology. It's not designated as a high-priority measure, but there it is, item No. 177, tying clinicians at least indirectly to a TTT approach for their Medicare patients: the percentage of patients aged 18 years and older with a diagnosis of RA who have an assessment and classification of disease activity within 12 months.

Slow on the uptake

Despite the data and the dictum, however, TTT remains an outlier in the United States. The most recent studies suggest that most U.S. rheumatologists do not employ it.

Dr. Curtis is the primary author on one of the newest studies, which employed a 26-question survey about the use of a quantitative measurement in RA patients and attitudes about using it (J Rheumatol. 2018 Jan;45[1]:40-4). The survey went out to almost 2,000 rheumatologists; 439 returned it.

Overall, just 44% said they "always practice in a treat-to-target manner, regularly using a scoring metric." Younger physicians, those in group practices, and those who made regular use of TNF inhibitors were more likely to practice this way. A total of 35% said they never used a quantitative metric for their RA patients.

"The No. 1 reason given about not using them is that it's too time-consuming and not easy enough," Dr. Curtis said in an interview. "Logistics is a key barrier." Busy clinicians don't want to spend time entering data into an electronic medical record, and there aren't easy ways to merge a specific

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DAM with a practice's chosen EHR. "There's a hassle factor, for sure."

The age gap was interesting but not unexpected, he said. "Older rheumatologists say they like to go by their gut, by a clinical gestalt," Dr. Curtis said, while younger physicians without decades of experience are more comfortable with such clinical tools. For some, age contributes to a kind of clinical inertia. "Doctors trained in an earlier era might be more tolerant of patients not doing as well. I'm a younger physician, and I have never known the era of not having biologics. They lived and practiced in that era, so their spectrum of what's 'normal' and acceptable for patient progress may be wider."

The research of Daniel H. Solomon, MD, of Brigham and Women's University, Boston, tells a similar story.

He and his colleagues investigated whether a 9-month group-based learning collaborative could improve TTT numbers among 46 rheumatologists at 11 practices. The endpoint was a combination of four TTT principles: recording a disease target, recording a disease activity measure, engaging in shared decision making, and changing treatment if disease target hasn't been reached.

At baseline, 64% of visits to these rheumatologists had none of the TTT components present, 33% had one component, and 2.3% had two components; just 3% of the visits included all of the components (Arthritis Care Res. 2017 Aug 22. doi: 10.1002/acr.23343).

The project consisted of nine sessions, most conducted by webinar. The entire practice team took part, learning the principles and practices of TTT, identifying their unique barriers to implementing it, and coming up with their unique way of integrating TTT into their practice. It was fairly successful, Dr. Solomon said in an interview. After the intervention, 57% of the exposed practices had incorporated TTT.

In January, Dr. Solomon published a follow-up study of the stability of those changes (Arthritis Care Res. 2018 Jan 5. doi: 10.1002/acr.23508). He was impressed with the results. Most sites from the first cohort had sustained the improvement during the second training period (52%).

"We found that people could implement it effectively when we gave them the tools to do it," he said. "It's definitely achievable, but it takes some commitment and guidance, and the realization that everyone can contribute to success in a collaborative manner."

Technology, or the lack of it

Many rheumatologists view TTT and the consistent measuring it involves as just one more headache-inducing time suck, said John Cush, MD.

Dr. Cush, director of clinical rheumatology at Baylor Scott & White Research Institute, Dallas, does employ TTT strategies. "I believe TTT makes you a smarter doctor and gives your patient the best chances of improvement. It pushes both of us out of complacency when we're tempted to go with the devil we know. Yes, change is a radical thing, but in RA change is almost always good. I think until people are forced to do that, they won't realize the benefit."

Dr. Cush

But at the same time, he freely admits that the time spent ticking boxes on a paper form or a computer, and being forced to report those to a federal agency, could be the camel-breaking straw for many.

"It's going down the path of what makes medicine sucky," he said in an interview. "Bean counters telling me how to practice medicine, who think they can use this TTT to manage what I do. I don't need more people trying to regulate my life."

Dr. Cush has conducted surveys on physician burnout and depression. "Administrative tasks and electronic records are a large part why 24% of people are burning out in medicine."

Right now, there's no easy way for many rheumatologists to incorporate regular DAM measures into their EHR system. The extra steps needed to get them there impede physician compliance with the strategy, he and Dr. Curtis agreed. But, Dr. Curtis said, there's an app for that.

He is the developer of the Rheumatic Disease Activity (READY) measure. The iPad/iPhone app, which is free to download in the app store, is an electronic measurement tool that efficiently captures patient-reported outcomes in RA and other rheumatic conditions.

"This tool really makes it much easier to collect DAM from patients," Dr. Curtis said. "It is designed for the doc who says, 'I would take data from patients; just make it easy for me to do that.' It takes 5-10 minutes to complete, and you get information about pain, fatigue, anxiety, and social interactions and, he said, can be easily integrated into work flow.

On a practice-provided device, the patient answers questions validated on the National Institutes of Health Patient-Reported Outcomes Measurement Information System. It includes a number of electronically scored and validated DAMs and provides trend charts to visualize longitudinal score data and track patient health status over multiple encounters. There are also places to record data about current and past medications.

"The docs input no data, which is the usual deal-killer. All they have to do is figure out how to integrate it into the work flow."

The ACR is also working on the technology issue, said Kaleb Michaud, PhD, of the University of Nebraska in Omaha.

"ACR has been communicating with the major EMR providers out there to make this easier. We are seeing some tools for iPads and smartphones, as well as paper tools."

The ACR RISE Registry is another option, said Evan Leibowitz, MD, a rheumatologist in Midland Park, N.J., and an ACR spokesperson.

"RISE is open to all rheumatologists in this country, and ACR has tried to make it as easy as possible. It can interface with most EMRs. All the physician does is collect the data, and it gets transferred to a HIPAA-protected database where it's

analyzed and presented back to the doctors so they can look at all their metrics. It's currently the least painful way to get involved in a registry, I think."

But just as techies are rolling out ways to interface DAMs and EHRs,

Dr. Kaleb Michaud: ACR has been communicating with the major EMR providers to make collecting patients' data easier.

medicine is marching forward. A new blood test called VECTRA DA measures 12 inflammatory biomarkers and may provide all the information needed to make treatment escalation decisions, Dr. Leibowitz said.

"The least painful option will probably be the VECTRA DA score. It's a single blood test, which we can do easily since we already draw blood. Rather than filling out a RAPID3 [Routine Assessment of Patient Index Data 3] or a CDAI [Clinical Disease Activity Index], we draw the blood, send it to the company, [and] they return us a score that indicates low, moderate, or high disease activity."

The results of studies have shown that not only is the VECTRA DA score a good clinical management tool, predicting responses, it can also predict impending relapse.

TTT challenges for patients

Rheumatologists are not the only ones reluctant to embrace TTT. It challenges patients as well, in a number of ways.

"Patients have to be willing to change treatments as often as you need them to, and that can be every 3-6 months, or even more quickly," Dr. Curtis said. "The cost can be a factor. And a lot of patients are risk averse. They feel there may be more of a downside to switching than a benefit to be gained, especially if they've had RA for a while. Maybe they're feeling a lot better than they were; their disease is still active, but they don't feel bad enough to want to change medications."

Researchers have explored these questions.

Last year, Dr. Michaud published a survey of 48 RA patients who were interviewed about their experiences with DMARDs and the feelings that would prompt them to comply with a treatment regimen – or resist one (Arthritis Care Res. 2017 Jun 2. doi: 10.1002/acr.23301).

"For patients' motivations to accept treatment regimens, two themes emerged," said Dr. Michaud, who is also codirector of the National Data Bank for Rheumatic Diseases. "One, the desire to return to a 'normal' life and, two, the fear of future disability due to RA. For motivations to resist treatment regimens, five themes emerged: fear of medications, maintaining control over health, denial of sick identity, disappointment with treatment, and feeling overwhelmed by the cognitive burden of deciding."

The findings confirm one of TTT's core tenets: involving patients in treatment decisions, Dr. Michaud said in an interview. "A lot of patients in my studies have reached a place of 'OKness' with their RA. The don't want to change what they feel is working. They're afraid of getting worse because they've been there and know what that can be."

Rapid change-ups to new medications are especially intimidating to long-term patients, he said. "This is a very important aspect of resistance to change. The side effects of these medications, both major and minor, are not something that people want to experience."

Physicians and patients often differ in their interpretation of a side effect, said Liana Fraenkel, MD, another rheumatologist who's exploring this area.

"As a physician, I'm worried about the rare and extremely rare adverse events – things that are really dreaded, that can be fatal. However, these happen in only a couple out of tens of thousands of patients. On the other hand, there are common side effects that occur in up to 20% of our patients. They're not a serious threat

Dr. Liana Fraenkel: Rheumatologists may undervalue common drug side effects.

to health, but they impact quality of life every day with nausea, dizziness, diarrhea, headache, and brain fog. As rheumatologists, we really undervalue these, and guess what? When we ask patients, it turns out that nausea and dizziness and diarrhea are not things that they want in their daily lives."

Dr. Fraenkel of Yale University, New Haven, Conn., explored this topic in a recently published survey of 1,273 RA patients that sought their concerns about taking triple therapy, biologics, and Janus kinase inhibitors (Ann Rheum Dis. 2017 Dec 15. doi: 10.1136/annrheumdis-2017-212407). The survey included seven medication attributes – administration, onset, bothersome side effects, serious infection, very rare side effects, amount of information, and cost – and sought to determine the relative effect of each attribute on patient preference for

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different treatment options.

"We found five distinct clusters" of patients, Dr. Fraenkel said in an interview. "I will admit I was surprised when I saw the largest group (38%) was most concerned about the cost of their medications. Our assumption is always that the rare and dreaded side effects are the most concerning, but for these patients, cost was the dominant issue. It's the No. 1 reason patients are noncompliant with their initial treatment recommendations. And with the cost of our biologics, it is a very big deal."

Her reaction pinpoints an important obstacle in shared decision making: physician bias. "I'd say the vast majority of us argue that the benefit of TTT outweighs the harms. We minimize inflammation, so patients will live longer with less disease impact. But how we get there should be up to the patient. My biases shouldn't come into play. The decision to intensify is different than the decision about how to intensify. This is where the back-and-forth comes in, making sure the patient understands the pros and cons of escalating or not.

"If she decided no, she doesn't incur the risk of a new medication, but she does incur the risk of progressing. The bottom line is that physicians should not bring their biases to the table but describe the facts, the importance of which will be different to different patients who have different goals."

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Real-world study finds treat-to-target benefits out to 5 years

BY JEFF EVANS
FROM CLINICAL RHEUMATOLOGY

A treat-to-target (TTT) strategy in daily clinical practice for patients with early rheumatoid arthritis proved successful in maintaining good disease- and patient-related outcomes over a 5-year period at two rheumatology clinics in the Netherlands.

The observational study builds on previous research on the long-term results of continuous application of TTT strategies in rheumatoid arthritis, for which there have been few published studies. "Long-term data from more recent randomized controlled clinical trials, using a [TTT] approach and biologicals, have shown good clinical outcomes. However, the generalizability of these results is hampered by the selection of specific patient groups in clinical trials and strict exclusion criteria. Patients seen in real-life practice may differ substantially from those in randomized clinical trials," first author Letty G.A. Versteeg of Medisch Spectrum Twente, Enschede, the Netherlands, and her colleagues wrote in Clinical Rheumatology.

The investigators examined outcomes for 229 patients with very early RA who enrolled in the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort during 2006-2009, which included 5 years of follow-up for 171 of the patients. These patients underwent a protocoled TTT strategy aimed at remission, defined as a 28-joint Disease Activity Score (DAS28) of less than 2.6.

"In previous publications on the [DREAM] remission induction cohort, successful implementation of [TTT] in daily clinical practice was demonstrated. Achieving remission within the first year of treatment was shown to be a realistic goal for an important proportion of patients," the authors wrote.

All patients started methotrexate monotherapy at an initial dosage of 15 mg/week that could be increased to a maximum dosage of 25 mg/week in week 8. Patients took folic acid on the second day after methotrexate.

By week 12, those with persistent disease activity added sulfasalazine, starting at 2,000 mg/day and increasing if necessary to a maximum of 3,000 mg/day at week 20. Patients whose DAS28 remained at 3.2 or greater at week 24 received a tumor necrosis factor inhibitor. Those who reached remission had no change in medication, and when remission lasted for at least 6 months, medication was gradually tapered and eventually discontinued.

Patients who had flares in which disease activity increased to a DAS28 of 2.6 and higher restarted their last effective medication or dosage, which could subsequently be intensified if necessary. Patients with comorbidities and contraindications for medication were not excluded because deviations from the protocol were allowed. The protocol also allowed concomitant treatment with NSAIDs, prednisolone at a dosage of less than 10 mg/day, and intra-articular corticosteroid injections.

The rate of DAS28-defined remission rose to 63% (126 of 199 patients) by the end of the first year, and only 5% had high disease activity at 24 weeks. The rate of remission remained stable over the next 4 years. This rate of remission was reflected as a drop from an overall mean DAS28 of 4.93 at baseline to 2.49 at 5 years. The majority of the drop in DAS28 occurred during the first 3 months (–1.63 points), and by the end of the first year of treatment, mean disease activity stayed below 2.6 on the DAS28.

The investigators saw a sustained remission at least once in 144 of the 171 patients with 5-year outcome data available, including sustained remission for 1 year or longer in 115. Median time to the first sustained remission proved to be 50 weeks, and half had this last less than 97 weeks and half more than 97 weeks.

During the 5-year follow-up, 17% of patients received treatment with biologics, with a median start of their first biologic at about 54 weeks after baseline.

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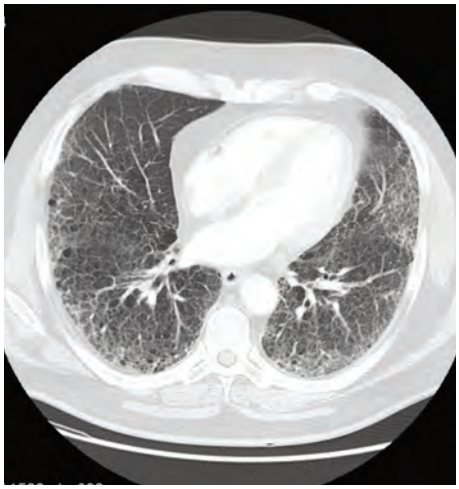
Genetic risk factor found for RA-associated interstitial lung disease

BY BRUCE JANCIN
REPORTING FROM THE ACR ANNUAL MEETING

CHICAGO – Rheumatoid arthritis–associated interstitial lung disease and idiopathic pulmonary fibrosis without RA share a common genetic underpinning whose hallmark is a gain-of-function MUC5B gene promoter variant that cranks up mucin production in the lungs, Pierre-Antoine Juge, MD, reported at the annual meeting of the American College of Rheumatology.

He presented a seven-country genetic case-control study of 620 patients with RA-associated interstitial lung disease (RA-ILD), 614 with RA but no ILD, and 5,448 unaffected controls. The key finding was that the MUC5B promoter variant rs35705950, already known to be the strongest genetic risk factor for idiopathic pulmonary fibrosis (IPF), also contributes substantially to the risk of RA-ILD.

Indeed, the presence of the MUC5B promoter variant in patients with RA proved to be associated with substantially higher risk of RA-ILD than the previously recognized risk factors for RA-ILD, including cigarette smoking and the human leukocyte antigen locus for RA, according to Dr. Juge, a rheumatologist at Bichat Hospital–Claude Bernard and Paris Diderot University.



Courtesy Assoc. Prof Frank Gaillard, Radiopaedia.org, rID: 12274

A CT demonstrates extensive pulmonary fibrosis in the mid and lower zones (note the extensive honeycombing).

MUC5B encodes for mucin production in the lungs. The increased risk of RA-ILD conferred by the presence of the MUC5B promoter variant was confined to the 41% of RA-ILD patients with a pattern of usual interstitial pneumonia (UIP) or possible UIP on high-resolution CT. The presence of the MUC5B promoter variant in RA patients was independently associated with an adjusted 6.1-fold increased risk of ILD with a UIP pattern on imaging – marked by honeycombing, reticular abnormalities, and subpleural involvement – compared with RA patients who didn't possess the gain-of-function MUC5B variant. The risk of other types of RA-ILD wasn't affected by the presence or absence of the MUC5B variant. The MUC5B promoter variant was not a risk factor for development of RA.

These findings have potentially important implications for clinical practice, given that clinically significant ILD is present in about 10% of all RA patients and occult ILD is detectable using high-resolution CT in up to half of individuals with RA, Dr. Juge observed. Detection of the MUC5B promoter variant could be used to screen patients with RA for preclinical ILD. Also, there is now a sound rationale to study drugs known to be effective for IPF as potential treatments for RA-ILD, he said.

Dr. Juge reported having no financial conflicts regarding the study, which was sponsored by the National Institutes of Health, the U.S. Department of Defense, the French Rheumatology Society, the Japanese Society for the Promotion of Science, Fondation Arthritis, and the Nina Ireland Program for Lung Health.

In conjunction with his presentation in Chicago, the study was published online in the New England Journal of Medicine (doi: 10.1056/NEJMoa1801562).

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SOURCE: Juge P-A et al. Arthritis Rheumatol. 2018;70(Suppl 10), Abstract 1819.

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This first biologic was used continuously for a median of 29 weeks, and close to one-third of patients who started a biologic switched to a second biologic after a median duration of 41 weeks on the first. About two-thirds did not need a second biologic. A total of 66% of patients who took a biologic had at least one period of sustained remission.

Functional disability improved overall at 5 years as determined by Health Assessment Questionnaire (HAQ) scores that were available for 107 patients. HAQ scores decreased from a median of 1.125 at baseline to 0.375 after 24 weeks (*P* less than .001), where they remained stable throughout the rest of follow-up. Overall, nearly 70% of the patients with available 5-year data had a change in their individual HAQ score that was clinically meaningful from baseline to 24 weeks.

"Our study describes long-term outcome of implementation and continuous application of [TTT] to RA patients in daily clinical practice. The outcomes are similar to or even better than the results of [TTT] randomized clinical trials, in which strict selection of patients and controlled conditions were followed. These 'real-life data' are of important additional value in the evidence for the effectiveness of a [TTT] approach in RA patients," the investigators concluded.

They had no disclosures to report.

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SOURCE: Versteeg LGA et al. Clin Rheumatol. 2018 Feb 1. doi: 10.1007/s10067-017-3962-5.

Methotrexate-induced pulmonary fibrosis risk examined in 10-year study

BY SARA FREEMAN
REPORTING FROM RHEUMATOLOGY 2018

LIVERPOOL, ENGLAND – A 10-year follow-up of patients with inflammatory arthritis has shown that methotrexate does not appear to increase the risk of pulmonary fibrosis.

"As rheumatologists, it's a really important message that methotrexate does not cause chronic pulmonary fibrosis and it should not be stopped because of pulmonary fibrosis," Julie Dawson, MD, said in an interview at the British Society for Rheumatology annual conference. "It's the rheumatoid arthritis. It's not the methotrexate."

Dr. Dawson, of St. Helens and Knowsley Teaching Hospitals NHS Trust, St. Helens, England, added that the current findings were consistent with her team's prior research looking at earlier time periods. There was also no correlation between the duration or dose of methotrexate used and the development of the lung disease, she said.

Sara Freeman/MDedge News

Dr. Julie Dawson: "As rheumatologists, it's a really important message that methotrexate does not cause chronic pulmonary fibrosis and it should not be stopped because of pulmonary fibrosis."

"If anything, the suggestion is you'd be more symptomatic if you delay using methotrexate," Dr. Dawson observed. If patients are not doing well on methotrexate, then perhaps adjusting therapy or changing to another drug would of course be the next step, but if patients are well controlled then "stopping it is the worst thing to do" for their arthritis, she said.

"This is of great clinical interest, and we can be reassured now about this, I think. This is really good, long-term data," said Devesh Mewar, MD, of Royal Liverpool and Broadgreen University Hospitals NHS Trust, in Liverpool, who was not involved in the research.

"We know that methotrexate is associated with a pneumonitis reaction, but there is no high-quality evidence that methotrexate is associated with a chronic pulmonary fibrosis" Dr. Dawson said, explaining the rationale

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VIEW ON THE NEWS

Study generates hypothesis but leaves incidence unknown

THE SUBJECT OF THIS RETROSPECTIVE study is of great interest. The authors point out that pulmonary fibrosis (as opposed to acute allergic reaction, which is extremely rare) is also extremely uncommon in patients using methotrexate over the long haul. Over 10 years, their data point to a 3.1% incidence of symptomatic pulmonary fibrosis.

The issue here is its generalizability. There were 63 patients who used methotrexate for 10 years or more and 88 who used it for 5 years or more, according to the poster. This must represent a highly selected population. For example, what percent of the total RA/psoriatic arthritis/"inflammatory arthritis" population do these patients represent; i.e., what is the denominator here? The authors stated that the 63 patients who stayed on methotrexate for 10 or more years represent 49% of the 129 patients on methotrexate overall in the study. This is a highly unusual datum, as most of the literature indicates that only 40% or less of patients stay on methotrexate for even 5 years. And this completely ignores the issue of adherence over this long a period; these patients must represent a truly minuscule percentage of the total if they actually stayed on methotrexate with even moderate adherence for 10 years.

Dr. Furst

Importantly, the authors point out that they had only four cases of symptomatic pulmonary fibrosis. Once more, this points to the highly selective group of patients seen, as this study does not examine patients with asymptomatic pulmonary fibrosis, including those with fibrosis on high-resolution CT of the lungs or chest film or evidence of abnormalities on pulmonary function tests, but who do not have sufficient symptoms ascribed to methotrexate to bring them to medical attention.

This is a nice hypothesis-generating study, but the actual incidence of methotrexate-induced lung fibrosis remains completely unknown. I heartily applaud their intention to start a prospective study to answer this interesting question.

Daniel E. Furst, MD, is professor of rheumatology at the University of Washington, Seattle, who also is affiliated with the University of California, Los Angeles, and the University of Florence (Italy). He was not involved with the study.

Complications cluster in inflammatory arthritis patients after total knee replacement

BY MITCHEL L. ZOLER
REPORTING FROM THE ACR ANNUAL MEETING

CHICAGO – Patients with an inflammatory arthritis had significantly higher rates of infections, transfusions, and readmissions following total knee replacement than did patients without inflammatory arthritis in a study presented at the annual meeting of the American College of Rheumatology.

A sampling of 137,550 U.S. patients who underwent total knee arthroplasty (TKA) during 2007-2016 showed that, among the 2% of these patients who had an inflammatory arthritis (IA), the rate of periprosthetic joint or wound infection while hospitalized or out to 30 days after surgery was a statistically significant 64% higher relative to patients without inflammatory arthritis, after adjustment for several confounders, Susan M. Goodman, MD, said at the meeting. The analysis also showed a statistically significant 46% higher relative rate of hospital readmission for any cause during the 90 days after surgery, and a significant 39% relative increase in blood transfusions during the 30 days after TKA in the IA patients.

Complications following TKA became a particular concern starting in 2013 when the Centers for Medicare & Medicaid Services began a program that penalized hospitals for outcomes such as excessive readmissions following selected types of hospitalizations and also with recent steps to bundle TKA reimbursement with related 90-day outcomes.

"These results have important implications for evolving bundled payment models" for TKA, said Dr. Goodman, a rheumatologist at the Hospital for Special Surgery in New York. "My concern is to ensure that patients with IA aren't penalized and can maintain access" to TKA despite recent policy moves by the CMS. Faced with potential disincentives to treat patients with an IA, "hospitals might cherry-pick patients," Dr. Goodman said in an interview. The new findings "are a reason for administrators to argue for patients with IA to come out of the cost bundle."

The investigators classified IA as a patient with a recorded diagnosis of rheumatoid arthritis, spondyloarthritis, or systemic lupus erythematosus (SLE) if the patient had also received treatment during the year before surgery with a disease-modifying antirheumatic drug, a biologic agent, or a drug that treats SLE.

Dr. Goodman had no disclosures.

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SOURCE: Richardson S et al. Arthritis Rheumatol. 2018;70(Suppl 10), Abstract 1932.

Continued from previous page

for the current study she presented during a poster session. Previous studies considered data for up to 5 years, she added, so the aim of the current study, therefore, was to look at the longer-term effect of methotrexate use on the incidence of pulmonary fibrosis.

Data on 129 patients who had started treatment with methotrexate from 2004 to 2007 were analyzed, of whom 63 (49%) had stayed on methotrexate for 10 or more years. Most (82%) had been given methotrexate to treat rheumatoid arthritis, with other indications including inflammatory arthritis (5.4%) and psoriatic arthritis (4.7%).

"Practice was different 10 years ago, so just 56% of patients commenced methotrexate within the first year of the diagnosis of rheumatoid arthritis," she said.

Only four cases of symptomatic pulmonary fibrosis were seen, all in the RA patients, and three of these were in patients who had started methotrexate over 1 year after their diagnosis. The incidence of 3.8% seen in the study matches the expected incidence of pulmonary fibrosis in RA and was actually "at the lower end of the expected incidence," Dr. Dawson said. Previous studies have suggested an incidence rate of RA-associated interstitial lung disease of about 3%-7%.

All of the pulmonary fibrosis cases had occurred in men and 75% were seropositive for rheumatoid factor. The mean duration of RA at the time of onset of pulmonary fibrosis was 7.8 years, and the usual interstitial pattern of fibrosis was seen. The 125 patients without pulmonary fibrosis had taken methotrexate for a mean of 8 years at a mean final weekly dose of 16.3 mg, compared with a mean of 6 years at a mean dose of 18.1 mg per week in the 4 patients with pulmonary fibrosis.

One of the next steps is to look at cases where methotrexate has been stopped and the effects of that on pulmonary fibrosis and disease activity. In Dr. Dawson's experience, stopping methotrexate just affects the management of the arthritis and had no difference to the progression of pulmonary fibrosis.

If patients start to experience any lung symptoms while continuing methotrexate, such as shortness of breath, then they would need to be assessed and undergo lung function tests to monitor their condition.

This is something the British Rheumatoid Interstitial Lung network plans to investigate treatment with an antifibrotic agent such as pirfenidone in a placebo-controlled study of RA patients with fibrotic lung disease. "We're looking to see if antifibrotic agents are going to slow the disease as it does in idiopathic pulmonary fibrosis, which is obviously quite exciting when it's such a hard condition to treat," said Dr. Dawson, who will be one of the study's investigators.

Dr. Dawson had no conflicts of interest to disclose. Dr. Mewar was not involved in the study and had nothing to disclose.

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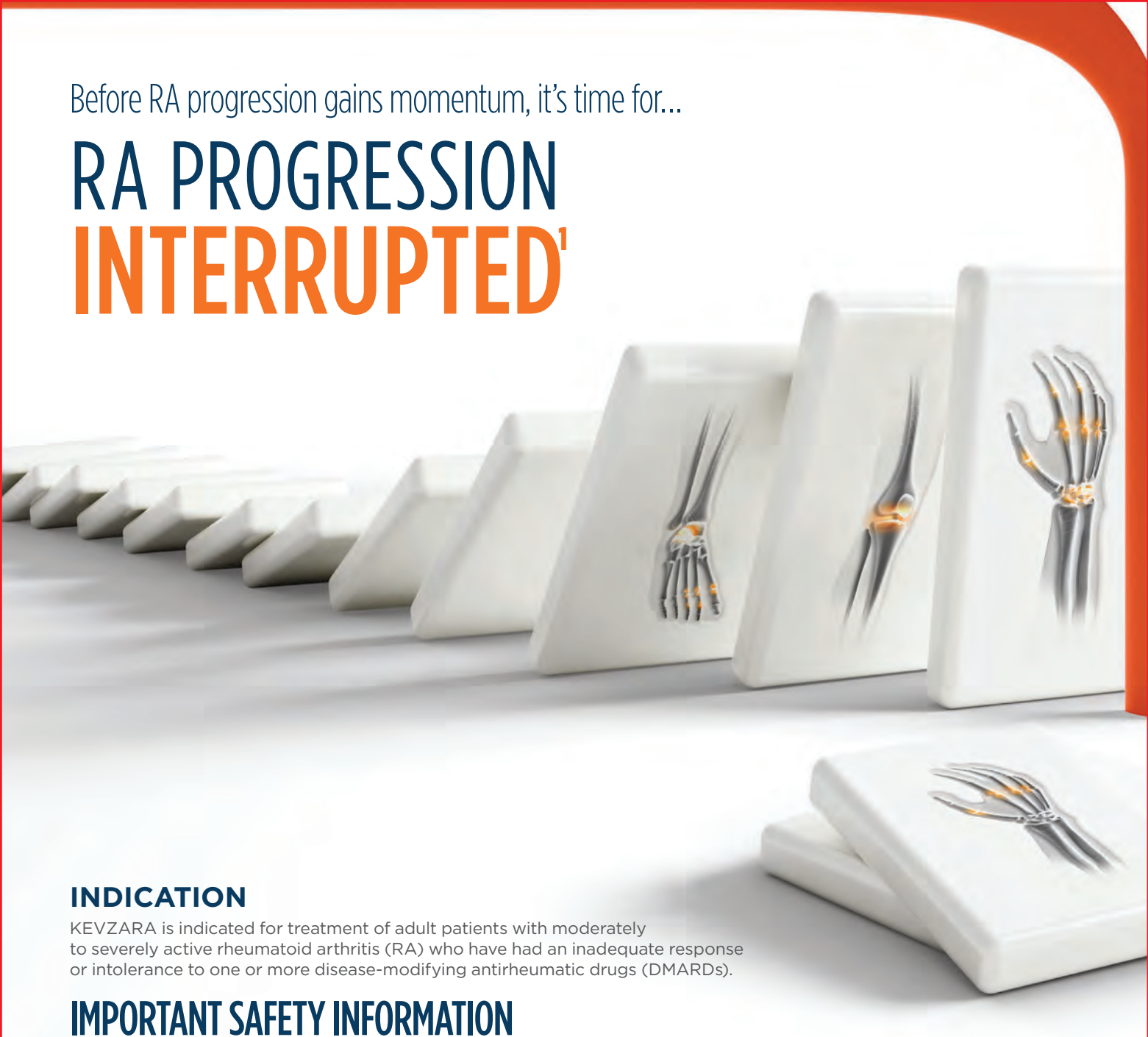
SOURCE: Dawson J et al. Rheumatology. 2018;57(Suppl. 3):key075.470.

Before RA progression gains momentum, it's time for...

RA PROGRESSION INTERRUPTED[1]



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.

KEVZARA IS AN IL-6 RECEPTOR INHIBITOR WITH THE STRENGTH TO INHIBIT RA PROGRESSION[1]

- Inhibition of joint damage progression in MTX-IR patients[1]
- Consistent efficacy demonstrated in TNF-IR and MTX-IR patients[1]
- Available in 2 dosage strengths as a subcutaneous injection[1]
  - Recommended dose is 200 mg every 2 weeks
- KevzaraConnect®—comprehensive support helps enable patient access and minimize barriers to KEVZARA

KEVZARA®
(sarilumab) injection
200 mg | 150 mg

No structural damage progression was observed at week 52 in 55.6% and in 47.8% of patients receiving KEVZARA 200 mg + MTX or 150 mg + MTX, compared with 38.7% of patients receiving placebo + MTX (defined by change in Total Sharp Score ≤0).[1]

See Trial Designs on following page.

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

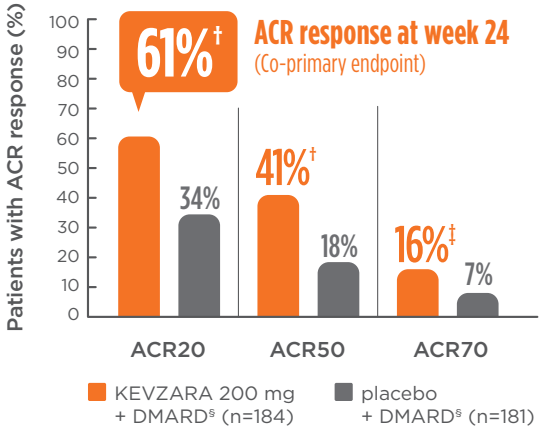
Please visit **KEVZARAhcp.com**

SANOFI GENZYME REGENERON

ROBUST EFFICACY IN PATIENTS WITH A HISTORY OF INADEQUATE RESPONSE[1]

CONSISTENT IMPROVEMENTS IN ACR RESPONSE ACROSS TNF-IR* AND[1,2]

TARGET (TNF-IR)



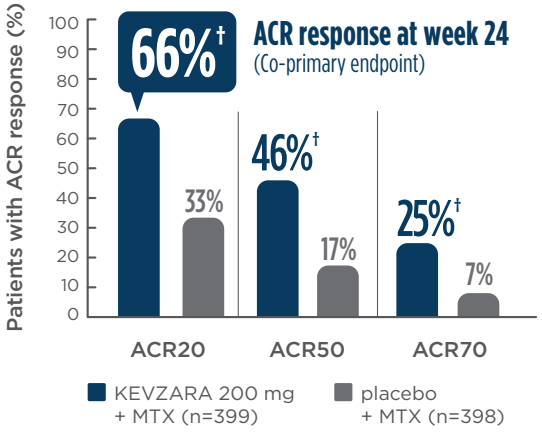
TARGET Study Design: A 24-week, randomized, double-blind, parallel group, placebo-controlled, multicenter study (N=546) assessing the efficacy and safety of KEVZARA 200 mg and 150 mg added to background conventional DMARD(s) in adult patients with moderate to severe active RA (≥6 months duration) with 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.

- With KEVZARA 150 mg + DMARD, 56%† of patients achieved ACR20 response, 37%† achieved ACR50 response, and 20%‖ achieved ACR70 response at week 24 (n=181)

*After 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; §DMARDs in TARGET include MTX, sulfasalazine, leflunomide, and/or hydroxychloroquine; ‖*P*<0.001.

MTX-IR* POPULATIONS[1,3]

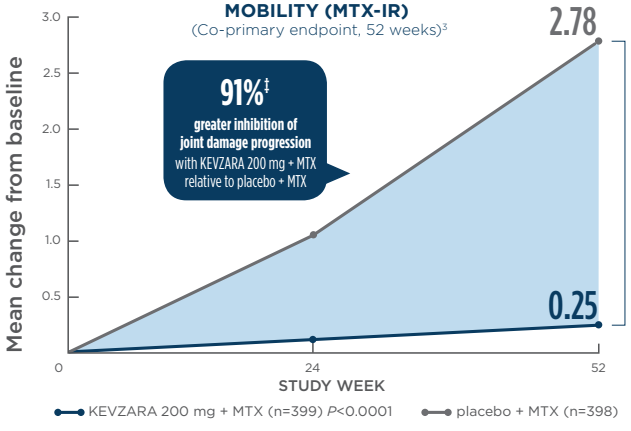
MOBILITY (MTX-IR)



- With KEVZARA 150 mg + MTX, 58%† of patients achieved ACR20 response, 37%† achieved ACR50 response, and 20%† achieved ACR70 response at week 24 (n=400)

*After week 16 in MOBILITY, patients with an inadequate response could have been treated with open-label KEVZARA 200 mg every 2 weeks.
†*P*<0.0001.
MTX-IR=inadequate response.

INHIBIT PROGRESSION OF JOINT DAMAGE[1,3]



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

- 68%‡ greater inhibition of joint damage progression with KEVZARA 150 mg + MTX at week 52 relative to placebo + MTX[1]
  - KEVZARA 150 mg + MTX provided an absolute difference of −1.88 units in mean mTSS relative to placebo + MTX

‡Based on post hoc comparisons of mean change in mTSS per treatment group.
CI=confidence interval.
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.

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

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.
- ***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.
- ***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).

References: 1. KEVZARA [prescribing information]. Bridgewater, NJ: Sanofi/Regeneron Pharmaceuticals, Inc; 2018. **2.** 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. **3.** 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.

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

KEVZARA is available by prescription only.

SANOFI GENZYME REGENERON

SAUS.SARI.18.09.5552

KEVZARA®
(sarilumab) injection
200 mg | 150 mg

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%	0.7%

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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High-dose flu vaccine in RA patients beats standard dose

BY SHARON WORCESTER
REPORTING FROM THE ACR ANNUAL MEETING

CHICAGO – The administration of high-dose vs. standard-dose influenza vaccine provided substantially better immune responses in seropositive rheumatoid arthritis patients in a randomized, active-controlled trial.

High-dose trivalent influenza vaccine is known to improve immune responses in the elderly, but the current findings, which were presented at the annual meeting of the American College of Rheumatology, are the first to document a successful intervention to enhance vaccine responses in immunocompromised patients, according to Inés Colmegna, MD, of McGill University, Montreal.

MDedge News

Dr. Inés Colmegna: Treatment in all groups was safe, with no differences in adverse events between vaccine groups, and none of the adverse events were related to treatment.

Dr. Colmegna and her colleagues assessed antibody responses to either standard-dose (15 mcg of hemagglutinin per strain) quadrivalent inactivated influenza vaccine (SD-QIV) or high-dose (60 mcg of hemagglutinin per strain) trivalent inactivated influenza vaccine (HD-TIV) in 140 and 139 patients, respectively.

Seroprotection rates prior to vaccination were comparable in the two groups, but the high-dose recipients had consistently higher overall responses to vaccination.

Seroconversion rates were 22.3% vs. 8.6% (odds ratio, 2.93) for the H3N2 strain (A/HongKong/4801/2014), and 44.6% vs. 28.6% (OR, 1.93) for the B Victoria Lin strain (B/Brisbane/60/2008). For the H1N1 strain A/California/7/2009 in 2016-2017 and closely related A/Michigan/45/2015 in 2017-2018, the seroconversion rates were 51.1% vs. 30.0% (OR, 2.91) and 46.4% vs. 24.6% (OR, 2.79), respectively. Seroprotection rates for the H3N2 strain were 48.5% vs. 30.9%, and for the B Victoria Lin strain, 60.0% vs. 50.7%. The seroprotection rates for the H1N1 strains together were and 80.4% vs. 73.5%, Dr. Colmegna said.

Seroconversion was defined as at least a fourfold serum hemagglutination inhibition (HI) antibody increase from prevaccination level (day 0), and seroprotection was defined as percent with HI titers of 1:40 or greater at postvaccination day 28.

After the researchers controlled for age, vaccine type, treatment type in the 3 months prior to vaccination and during the study period, Charlson comorbidity index, and RA duration, the only significant predictors of vaccine seroresponse were vaccine dose and age.

The findings are notable because RA patients have a nearly threefold increase in the risk of contracting influenza infection or related illness, compared with age-matched healthy controls, because of "inherent immune dysfunction associated with RA, comorbidities, the age of our patients, and immunosuppressive therapy," Dr. Colmegna said.

For this reason, RA patients are a priority group for annual vaccination. However, while vaccination remains the most effective method for preventing influenza and its associated complications, vaccine-induced antibody responses and protection in RA are suboptimal, she explained, noting that this puts them at increased risk for severe influenza.

"There is a high priority to develop new approaches to try to decrease this risk," she said.

It was unknown whether HD-TIV – the only currently available high-dose influenza vaccine – would safely enhance antibody production in RA as it does in the elderly, so she and her colleagues recruited patients from a tertiary care center during the 2016-2017 and 2017-2018 Northern Hemisphere influenza seasons for this study.

The mean age of the patients was 61 years, and 80% were women. All were on stable treatment with either disease-modifying antirheumatic drugs (DMARDs) or biologics for at least 3 months prior to vaccination; treatment types included DMARDs in 138 patients (49.5%), anticytokine therapy in 92 patients (33%), and anti–B-cell therapy and small molecules in 49 patients (17.6%). An analysis by treatment type showed a possible reduction in the rate of seroconversion in patients who received anti–B-cell therapy and small molecules, but the number of patients in the group was too small to make definitive conclusions, Dr. Colmegna said.

Treatment in all groups was safe, with no differences in adverse events between those receiving high- or standard-dose vaccine, and none of the adverse events were related to treatment. The high-dose vaccine also was not associated with an increase in disease activity.

"We believe that these results will likely change clinical practice," she concluded.

Dr. Colmegna reported having no disclosures.

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SOURCE: Colmegna I et al. Arthritis Rheumatol. 2018;70(Suppl 10), Abstract 837.

Aim for remission, not low disease activity, in rheumatoid arthritis

BY SARA FREEMAN
REPORTING FROM RHEUMATOLOGY 2018

LIVERPOOL, ENGLAND – For treatment to target in RA, the aim should be to get patients into remission and not just achieve low disease activity, according to the conclusion of a study presented at the British Society for Rheumatology annual conference.

The study showed clear differences in functional and quality of life outcomes over time when comparing patients who achieved remission with those who achieved low disease activity.

Not only were better scores on the Health Assessment Questionnaire (HAQ) seen if remission were achieved rather than low disease activity, but also better scores were recorded using the Short Form–36 (SF-36) mental component and physical components.

Indeed, from baseline assessments to 12 months follow-up, HAQ scores fell from an average of about 0.8 for those in remission and 0.9 for those with a low disease activity index to approximately 0.4 and 0.6, respectively.

The physical component score of the SF-36 also improved from around 35 and 30 at baseline in the remission and low disease activity groups to just above 40 and just under 35, respectively, at 12 months.

Baseline SF-36 mental component scores were around 51 and 49 in each group, respectively, at baseline but improved to around 55 with remission and remained steady in the low disease activity group at 12 months.

"This is something you often don't see," observed Sam Norton, PhD, who presented the findings on behalf of the lead author Elena Nikiphorou, MD. Dr. Norton is a senior lecturer in the department of health psychology at King's College London whose research interests lie in studying the psychological well-being and illness outcomes in rheumatoid arthritis and other chronic physical illnesses.

"Of course, there could be a bit of reverse causality with people with good mental health being more likely to hit remission, which is why you can see there is a gap at baseline as well," he said.

The researchers used data on 2,701 patients who were enrolled in the Early Rheumatoid Arthritis Network (ERAN) and Early Rheumatoid Arthritis Study (ERAS) cohorts. The research question was whether achieving low disease activity was an acceptable target in rheumatoid arthritis, and if disease outcomes made a difference to those who achieved remission.

The mean age of participants was 55 years in ERAS and 57 years in ERAN, with a similar percentage of female participants (67%), and slightly better baseline HAQ and Disease Activity Scale scores in the ERAN cohort, which is to be expected, Dr. Norton said, as this was a later-recruited population of patients (2002-2013 vs. 1986-2000 for ERAS).

Disease activity was categorized in three ways: firstly, remission and low disease activity over 1-5 years were defined as mean DAS28 score of less than 2.6 and a score of 2.6-3.2, respectively. Secondly, sustained low disease activity or remission was considered over 1-2 years, and thirdly, Boolean remission over 1-2 years, which are strict criteria of remission to meet.

Overall, 23.4% of patients achieved remission and 13.7% achieved low disease activity, and a respective 10.3% and 13.7% met criteria for sustained remission or sustained low disease activity. Just 3.4% met Boolean criteria for remission.

"The key messages are: There is a really important difference between remission and low disease activity score categories and that treating people to a remission target means they will do better in terms of quality of life outcomes over time compared to just stopping at a low disease activity," Dr. Norton noted.

However, he noted that there will likely be a relatively small proportion of patients that will achieve the strictest definition of remission, and perhaps different targets need to be set for those with comorbidities or who are older.

Dr. Norton and his coauthors had nothing to disclose.

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SOURCE: Nikiphorou E et al. Rheumatology. 2018;57(Suppl. 3):key075.189.

Rheumatoid arthritis

"Treating people to a remission target means they will do better in terms of quality of life outcomes over time."

After 12 months

Health Assessment Questionnaire scores: **0.4** for those in remission and **0.6** for those with low disease activity.

Short Form–36 scores: just above **40** for those in remisison and just under **35** for those with low disease activity.

MDedge News

Source: Sam Norton, PhD

High RA biologic drug levels linked with more infections

BY MITCHEL L. ZOLER
REPORTING FROM THE EULAR 2018 CONGRESS

AMSTERDAM – Patients with rheumatoid arthritis who had a high serum level of biologic immunomodulatory drugs had a statistically significant 51% higher rate of infection during their first year on the drug, compared with RA patients who maintained usual or low serum levels of the same drugs, according to an analysis of 703 U.K. patients in a national database.

The results suggest that, once patients with rheumatoid arthritis go into remission on a higher dosage of biologic agents that produce a high serum level "dose tapering may lower their risk of infection," Meghna Jani, MD, said at the European Congress of Rheumatology.

This apparent relationship between higher biologic drug levels and increased infections "may be another reason to measure drug levels in patients; it could make their treatment safer, as well as save money," said John D. Isaacs, MD, a professor of clinical rheumatology at Newcastle University in Newcastle upon Tyne, England, who was a coauthor on the study.

The study used data and specimens collected in two separate, prospective U.K. studies: the British Society for Rheumatology Biologics Register-RA, which had data from more than 20,000 U.K. patients with RA who started treatment with a biologic agent, and BRAGGSS (Biologics in Rheumatoid Arthritis and Genetics and Genomics Study Syndicate), a national prospective cohort of 3,000 RA patients who had serum specimens drawn at 3, 6, and 12 months after starting biologic drug treatment and tested by an immunoassay for the concentration of the drug each patient received.

The analysis focused on 703 patients for whom there were data while they were on treatment with any of five biologic drugs: the tumor necrosis factor inhibitors adalimumab (Humira; 179 patients), certolizumab (Cimzia; 120 patients), etanercept (Enbrel; 286 patients), and infliximab (Remicade; 14 patients) and the interleukin-6 blocker tocilizumab (Actemra; 104 patients).

Dr. Meghna Jani: Tapering may be worthwhile in remission on a higher dosage that produces a high serum level.

Photos Mitchel L. Zoler/MDedge News

Dr. John D. Isaacs: The observed relationship "may be another reason to measure drug levels in patients."

Dr. Jani and her associates considered serum levels that exceeded the following thresholds to categorize patients as having a high drug level: 8 mcg/mL adalimumab, 25 mcg/mL certolizumab, 4 mcg/mL etanercept, 4 mcg/mL infliximab, and 4 mcg/mL tocilizumab. The patients averaged about 59 years old, about three-quarters were women, and they had been diagnosed with RA for approximately 5-7 years. About 22% were also on treatment with a steroid, and most patients had not received prior treatment with a biologic agent.

The researchers tallied 229 diagnosed infections in the subgroup with high serum levels of their biologic drug, and 63 infections in those with levels below this threshold. After adjustment for age, sex, methotrexate use, and disease activity score, patients with high serum levels of their biologic drug had a 51% higher rate of all infections than did patients with levels that fell below the high-level threshold, reported Dr. Jani, a rheumatologist at Manchester (England) University. Analysis of the accumulation of infections over the course of 1 year of follow-up showed that this difference in infection rates became apparent after about 2 months of exposure and then began to diverge more sharply after about 5 months of exposure.

The results also showed that the rate of serious infections – defined as those resulting in the use of intravenous antibiotics, hospitalization, or death – were similar in the two subgroups. The types of infections and their relative frequencies were also roughly similar in the two subgroups. Lower respiratory infections were the most common infection in both subgroups, followed by infections of the upper respiratory tract, urinary tract, and skin as the next three most common infections in both subgroups.

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SOURCE: Jani M et al. Ann Rheum Dis. 2018;77(Suppl 2), Abstract 163.

TNF inhibitor linked to one-third drop in total mortality

BY MITCHEL L. ZOLER
REPORTING FROM THE EULAR 2018 CONGRESS

AMSTERDAM – Patients treated with a tumor necrosis factor inhibitor for any indication had their mortality rate cut by about one-third, compared with the general population, in a combined analysis of safety findings from 78 trials that involved nearly 30,000 patients.

This first indication that treatment with a tumor necrosis factor inhibitor (TNFi) significantly cut overall mortality became apparent only because of the very large number of patients and patient-years of treatment analyzed, and is likely a real effect – not an artifact – that's probably linked in part to the anti-inflammatory effect from treatment and it's favorable impact on cardiovascular disease events, Gerd R. Burmester, MD, said at the European Congress of Rheumatology.

The cut in overall mortality might also partially result from a "healthy cohort effect," in which patients enrolled in trials pay more attention to their diet and other aspects of a healthy lifestyle, compared with the general population. But Dr. Burmester cited the recent results from the CANTOS trial that showed treatment with the anti-inflammatory drug canakinumab (Ilaris) was linked with a significant 12% relative reduction in cardiovascular death, myocardial infarction, and stroke (N Engl J Med. 2017 Sep 21;377[12]:1119-31).

"It may be that the anticytokine effect of TNFi works the same way as canakinumab," Dr. Burmester said in an interview.

The results also confirmed previous reports, based on trial data from fewer numbers of TNFi-treated patients, of low rates of serious infections and malignancies, said Dr. Burmester, professor and director of the department of rheumatology and clinical immunology at Charité Medical University in Berlin.

The data he presented came from both randomized trials and open-label studies of adalimumab (Humira) conducted in several countries worldwide through the end of 2016. The various studies enrolled a total of 29,987 patients treated with adalimumab for 56,951 patient-years who had any of 11 different diseases, including rheumatologic, gastrointestinal, and dermatologic diseases. The most common condition treated in the studies was rheumatoid arthritis (in 33 of the 78 studies) followed by psoriasis (13 studies), and Crohn's disease (11 studies).

Mitchel L. Zoler/MDedge News

Dr. Gerd R. Burmester: The observed mortality reduction linked with TNFi treatment is likely a class effect.

The studies included 9,363 patients treated for at least 2 years, and 4,003 patients treated for at least 5 years. The median duration of adalimumab exposure was 0.7 years and the maximum exposure was just over 12 years.

The overall rate of serious infections in treated patients was 3.7 per 100 patient-years. The most common serious infections were pneumonia, at a rate of 0.6 per 100 patient-years, followed by cellulitis, at a rate of 0.2 per 100 patient-years. Active tuberculosis infections also occurred at a rate of 0.2 per 100 patient-years. Malignancies occurred at a rate of 0.6 per 100 patient-years. These rates were similar to those reported by Dr. Burmester and his associates in 2013 using data from a small pool of patients – 23,458 – enrolled in 71 studies of adalimumab (Ann Rheum Dis. 2013 Apr;72[4]:517-24).

In the current study, Dr. Burmester and his coauthors analyzed the observed mortality rate of the adalimumab-treated patients against the mortality rates for the general populations in the various countries in which the studies were run, based on World Health Organization statistics for the period 1997-2006, and adjusted so that the age and sex of the comparison general populations matched the age and sex of the treated patients. This analysis showed an overall, statistically significant mortality reduction in patients receiving adalimumab of 35%, which was consistent in both the subgroups of men and women.

The observed mortality reduction linked with TNFi treatment is likely a class effect, Dr. Burmester said, although similar analyses have not been conducted using data from patients treated with other TNFis. So far, he has been unsuccessful in getting similar, large-scale trial data from manufacturers of other TNFis that he has approached, but Dr. Burmester said he hopes to eventually receive these data so that he can perform an even larger analysis.

The study was sponsored by AbbVie, the company that markets adalimumab. Dr. Burmester has been a consultant to and speaker on behalf of AbbVie, as well as for Bristol-Myers Squibb, Merk, Pfizer, Roche, and UCB.

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SOURCE: Burmester GR et al. Ann Rheum Dis. 2018;77(Suppl 2):165, Abstract OP0233.


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RF-positive polyarticular JIA looks like adult RA

BY JIM KLING
FROM ARTHRITIS & RHEUMATOLOGY

New evidence suggests the rheumatoid factor–positive polyarticular subtype of juvenile idiopathic arthritis bears a close genetic resemblance to adult rheumatoid arthritis, lending support to the growing suspicion that, in arthritis, biological underpinnings are more important than age of onset when it comes to characterizing and, potentially, choosing treatments.

Previous work had shown that rheumatoid factor (RF)–negative patients have genetic risks similar to those of adults with RF-negative disease. "If the RF-negative patients in adult and childhood are similar, then maybe the RF-positive patients are similar in their genetic background as well. That's what this study was testing," study coauthor Anne M. Stevens, MD, PhD, division chief of rheumatology at the University of Washington, Seattle, said in an interview. The study was published online Feb. 9 in Arthritis & Rheumatology.

There are seven recognized categories of juvenile idiopathic arthritis (JIA), and all are believed to have genetic risk factors. Previously, the researchers used the Immunochip custom microarray to map 186 autoimmune disease–associated loci from 11 autoimmune phenotypes, including adult rheumatoid arthritis. In the current work, the researchers analyzed 340 RF-positive polyarticular JIA cases (292 females) and 14,412 controls (8,002 females) from Canada, Germany, Norway, United Kingdom, and the United States. RF-positive polyarticular disease accounts for about 5% of JIA cases, and its symptoms and presentations resemble adult RA.

The researchers found associations in the human leukocyte antigen (HLA) region. The most significant was found at rs3129769, near HLA-DRB1 ($P = 5.51 \times 10^{-31}$). This single nucleotide polymorphism (SNP) was in strong linkage disequilibrium (LD, $r^2 = 0.88$) with the rs660895 HLA-DRB1 SNP that has been reported in adult RA ($P = 2.14 \times 10^{-29}$).

The researchers examined links between RF-positive polyarticular JIA and the 27 SNPs that had been identified in the previous study of oligoarticular/RF-negative polyarticular JIA. Just 6 of those 27 SNPs were significantly associated with RF-positive polyarticular JIA (P less than .05). On the other hand, of 44 SNPs most strongly associated with RA, 19 were associated with RF-positive polyarticular JIA (P less than .05).

That suggests that RF-positive polyarticular JIA cases are different from other JIA cases. "They're more like adult patients than they're like child patients," said Dr. Stevens.

The researchers also compared the weighted genetic risk scores (wGRS) produced from the top RA loci to wGRS produced from the top oligoarticular/RF-negative polyarticular JIA loci. The wGRS from the top RA loci was a better predictor of RF-positive polyarticular JIA cases (area under the curve [AUC] = 0.71 versus AUC = 0.58; $P = 8.26 \times 10^{-33}$).

The wGRS from RA had similar success in predicting RF-positive polyarticular JIA and early-onset RA cases (AUC = 0.75; $P = .25$), but it fared worse in predicting late-onset RA (at 70 years or older, AUC = 0.62), compared with the wGRS from RF-positive polyarticular JIA ($P = 1.65 \times 10^{-5}$).

Those results suggest that RF-positive polyarticular JIA more closely resembles younger RA cases than older RA cases.

"If you consider early-onset RA patients, less than 29 years old when they develop RA, they look like JIA patients. But older RA patients, who are over 70 when they develop RA, they look like they totally have a different genetic background," Dr. Stevens said.

Bruce Jancin/MDedge News

Dr. Anne M. Stevens: "This weighted genetic risk score ... could be used to classify patients with one DNA sample."

The study could have clinical implications. The lead author, Anne Hinks, PhD, is a research fellow at the University of Manchester (England) and has led the charge to characterize JIA. The wGRS score she developed has the potential to help physicians diagnose, classify, and treat JIA patients. Currently, they must rely on the International League of Associations for Rheumatology criteria, which can take months to work through and may lead to misclassification diagnoses.

And in any case, the emerging genetic research suggests that the underlying genetics of JIA may be a better way to classify patients. "There's a lot of overlap and risk of misclassifying patients with the current system. This weighted genetic risk score that Dr. Hinks developed could be used to classify patients with one DNA sample. This is the kind of clinical test we need," Dr. Stevens said.

The study received funding from a range of government and private sources. Dr. Stevens has a patent licensed to Quest Diagnostics, is conducting research collaborations with Seattle Genetics and Kineta, and has received fellowship support from Pfizer.

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SOURCE: Hinks A et al. Arthritis Rheumatol. 2018 Feb 9. doi: 10.1002/art.40443.

Novel blood test brings RA prevention closer to reality

BY BRUCE JANCIN
REPORTING FROM THE ACR ANNUAL MEETING

CHICAGO – A positive B cell–clonality test in a peripheral blood sample predicts imminent onset of rheumatoid arthritis with a high degree of accuracy in at-risk individuals, Niek de Vries, MD, PhD, reported at the annual meeting of the American College of Rheumatology.

This finding, now confirmed twice over in separate validation studies, opens the door to trials of pharmacologic treatment aimed at preventing rheumatoid arthritis.

"In my view, a positive test might be an indication for preventive treatment and retesting at 1 year to evaluate the treatment effect," said Dr. de Vries, professor of rheumatology at the University of Amsterdam.

Many patients with RA experience a pre-RA phase marked by joint pain, the presence of RA-specific autoantibodies, IgM rheumatoid factor, and/or anti-citrullinated protein antibodies, but no synovial inflammation. The challenge in attempting to develop RA preventive strategies targeting this population is that only about 28% of them go on to develop RA within 3 years. Exposing the entire preclinical-phase population to powerful antirheumatic drugs to try to prevent RA in the minority who are actually headed for overt disease is not an attractive strategy.

That's why Dr. de Vries and his coinvestigators developed a method of B cell–receptor (BCR) analysis using polymerase chain reaction and next-generation sequencing techniques. They determined that, when a clone comprised more than 0.5% of the total B cell–receptor population, it can be considered an expanded or dominant clone. They then demonstrated that, when a patient in the pre-RA phase has five or more dominant clones in a peripheral blood sample, that can be considered a positive BCR test. In two published studies, they showed that a positive BCR test in the pre-RA stage accurately predicts onset of overt RA within the next several years (Ann Rheum Dis. 2017 Nov;76[11]:1924-30; Ann Rheum Dis. 2018;77:151). They have also shown that, at the time of RA onset, the BCR clones disappear from peripheral blood and reappear in the synovium.

Bruce Jancin/MDedge News

Dr. Niek de Vries: "I think it's very important to realize that what we test is the migration of B cells or plasmablast-like cells through the blood at the moment that we're testing."

At the ACR annual meeting, Dr. de Vries presented the results of a new BCR test validation study, this one involving 129 pre–RA-phase Dutch patients. The purpose of this study was to learn whether the BCR test is more predictive than clinical predictors such as the Risk Rule Model, and also to determine whether a higher number of dominant clones predicts RA onset even more accurately than the five-or-more clone threshold the investigators had been using. The answer to both questions proved to be yes.

Thirty-five percent of the 129 pre-RA subjects had a positive BCR test as defined by the presence of five or more expanded clones. A total of 75% of them went on to develop RA within the next 3 years. None of the BCR test–negative patients did. That result translated to a test sensitivity of 100%, a specificity of 87%, a positive predictive value of 71%, and a negative predictive value of 100%. A positive BCR blood test was associated with a 120-fold increased risk of an RA diagnosis within 3 years.

The investigators also compared outcomes in the 17% of study participants with a high degree of BCR test positivity, defined as the presence of nine or more expanded clones, versus the 18% of subjects whose positive BCR test had five to eight clones. Overall, 91% with a highly positive BCR test featuring nine or more clones developed RA within 3 years, compared with 55% of those with five to eight clones.

These findings permit categorization of pre-RA patients into three groups. Those with a negative BCR test can be reassured that their 3-year risk of developing RA is similar to the background risk in the general population. Those with a mid-range positive BCR test – that is, five to eight dominant clones – should probably be retested periodically, although the optimum interval is still under study. And patients with a highly positive BCR test might be candidates for preventive therapy.

Before RA-preventive therapy during the high-risk pre-RA phase can be introduced into routine clinical practice, however, several issues need to be resolved, Dr. de Vries continued. Although a single dose of rituximab (Rituxan) showed efficacy in a proof-of-concept study, that was off-label therapy. There is as yet no approved agent for prevention of RA in high-risk patients. Also, the risk/benefit ratio of preventive therapy will need to be determined. And rheumatologists will have to figure out how to identify

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Study links RA flares after joint replacement to disease activity, not medications

BY RANDY DOTINGA
FROM JOURNAL OF RHEUMATOLOGY

Patients with the most severe cases of rheumatoid arthritis are more likely to suffer flares after knee or hip replacement surgery, a new study finds, and it doesn't seem to matter whether they stop taking biologics before their operation.

"We found that the majority of patients had active disease at the time of surgery, contrary to prior statements that RA patients have inactive disease at the time they go for hip or knee replacement. In fact, the majority – 65% of the patients – reported a flare of RA within 6 weeks of surgery," lead author Susan M. Goodman, MD, of Cornell University and the Hospital for Special Surgery, New York, said in an interview. "Surprisingly, although more of the flaring patients were taking potent biologics that had been withheld preoperatively, the major risk factor for flares was their baseline disease activity."

The study appeared online March 15 in the Journal of Rheumatology.

According to Dr. Goodman, the researchers launched the study to better understand how medical decisions prior to joint replacement surgery affect the progress of RA afterward.

In terms of continuing RA drug treatment, she said, "the decision really hinges on the risk of infection versus the risk of flare, and we didn't know the usual course of events for these patients."

In addition, she said, "many doctors incorrectly think that the majority of patients with RA have 'burnt-out' or inactive disease at the time of hip or knee replacement surgery."

> "Surprisingly, although more of the flaring patients were taking potent biologics that had been withheld preoperatively, the **major risk factor for flares was their baseline disease activity.**"

For the study, the researchers prospectively followed 120 patients who were to undergo joint replacement surgery. (The researchers initially approached 354 patients, of whom 169 declined to participate. Another 65 were dropped from the study for various reasons, including 42 who did not sufficiently fill out questionnaires and were deleted from the final analysis.)

The researchers tracked the patients before surgery and for 6 weeks after surgery. A majority of the patients were female (83%) and white (81%), with a mean age of 62 and a median RA symptom duration of 15 years. A total of 44% underwent hip replacement surgery while the rest underwent knee replacement surgery. Just over half of the patients were taking biologics, which were stopped prior to surgery, while glucocorticoids and methotrexate were usually continued.

Just under two-thirds of the patients flared within the first 6 weeks after surgery. The researchers didn't find any connection between the flares and stopping biologics or using methotrexate. They did, however, link higher baseline RA activity to postsurgery flaring (odds ratio, 2.11; $P = .015$).

Dr. Goodman said that she and her colleagues continue to collect data to better understand flares and the link to disease severity. "The long-term implications of this are not yet known. We would like to know the effect on long-term functional outcome and complication rate."

The National Institutes of Health, the Weill Cornell Clinical Translational Science Center, and the Block Family Foundation supported the study. Dr. Goodman disclosed receiving research funding from Novartis and Roche.

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SOURCE: Goodman SM et al. J Rheumatol. 2018 Mar 15. doi: 10.3899/jrheum.170366.

Continued from previous page

these high-risk pre-RA individuals early, when preventive therapy is likely to most effective.

Several audience members observed that the Dutch investigators' BCR test using PCR and next-generation sequencing is technically complex. They asked if the BCR results might correlate with any far more readily available serologic tests. The answer is no, according to Dr. de Vries.

"I think it's very important to realize that what we test is the migration of B cells or plasmablast-like cells through the blood at the moment that we're testing. This is completely different from a serological assessment of antibody production by plasma cells which are present in the bone marrow, which changes very little despite effective treatment. In contrast, if we test B-cell migration while a patient gets corticosteroids we see an immediate disappearance of all these cells. So it's a different parameter," the rheumatologist explained.

The Dutch Arthritis Association funded the study. Dr. de Vries noted that he is a coinventor of the BCR test, the intellectual property rights for which belong to the University of Amsterdam. He receives research funding from Pfizer, Roche, Janssen, and GlaxoSmithKline.

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SOURCE: de Vries N et al. Arthritis Rheumatol. 2018;70(Suppl 10), Abstract 835.

Researchers identify three distinct clinical-histologic-genetic subtypes in RA

BY NICOLA GARRETT
FROM ARTHRITIS & RHEUMATOLOGY

Researchers have identified three different synovial subtypes of rheumatoid arthritis that exhibit different mechanisms of pain and correlate with specific clinical phenotypes.

The findings could be clinically meaningful and may help guide optimal treatment strategies for patients, as well as provide a better understanding of the cause of pain in patients with high tender and swollen joint counts but little tissue inflammation, according to the research team led by Dana E. Orange, MD, of the Hospital for Special Surgery and Rockefeller University in New York.

PositiveFocus/Thinkstock

The report was published in Arthritis & Rheumatology.

The assessment of the synovium in rheumatoid arthritis has the potential to provide guidance on optimal treatment strategies, they noted, but its classification has not yet factored into current diagnosis or treatment guidelines of RA.

In the study, the researchers analyzed clinical, histologic, and gene expression data from a cohort of 123 RA patients (106 of whom were women) who underwent arthroplasty at the Hospital for Special Surgery, and 6 osteoarthritis patients. About half of the RA patients were seropositive for rheumatoid factor and cyclic citrullinated peptides. The patients had a moderate Disease Activity Score in 28 joints (DAS28) of 3.8 on average despite their mean disease duration of 14 years.

In total, the research team analyzed 20 histologic features on 129 synovial tissue samples.

The researchers used machine learning integration to identify three distinct molecular subtypes of RA from a consensus clustering of the 500 most variable genes expressed in a subset of 45 synovial samples, including 39 from RA patients. The subtypes were high inflammatory, low inflammatory, and a mixed phenotype.

The researchers then took the histologic features that best corresponded to each subtype to develop a histology scoring algorithm that predicted the three gene expression subtypes (using only histology features), each of which were each associated with levels of erythrocyte sedimentation rate, C-reactive protein, and autoantibodies.

The histologic features that most strongly defined the high inflammatory subtype included three plasma cell features: binucleate plasma cells, plasma cell percentage, and Russell bodies. Patients with a high inflammatory synovial subtype also exhibited higher levels of markers of systemic inflammation and autoantibodies. For example, C-reactive protein was significantly correlated with pain in the high inflammatory group.

"This suggests that pain is associated with inflammation in patients with high inflammatory subtype and that pain may be driven by distinct mechanisms in the other patients," the study authors wrote.

The low inflammatory subgroup was characterized by high neuronal and glycoprotein gene expression. But in this group, pain scores were not associated with elevated inflammatory markers.

"It is interesting that this subtype is characterized by a paucity of inflammatory infiltrates, yet maintains high pain scores and multiple tender/swollen joints – this too is consistent with other findings of patients with established RA," the research team noted.

The mixed subtype shared features with both the high and low subtypes, the researchers said.

"Our work suggests that RA patients with longstanding disease and poor response to anti-inflammatory treatment may warrant synovial biopsy to determine their inflammatory subtype," the researchers concluded.

Several research institutions and the Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus Network, a public-private partnership involving several pharmaceutical companies, patient advocacy groups, and the National Institutes of Health, funded the study.

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SOURCE: Orange DE et al. Arthritis Rheumatol. 2018 Feb 22. doi: 10.1002/art.40428.

Obesity and weight loss both linked to RA disability

BY BIANCA NOGRADY
FROM ARTHRITIS CARE & RESEARCH

Both obesity and weight loss are associated with worsening disability from rheumatoid arthritis, new research suggests.

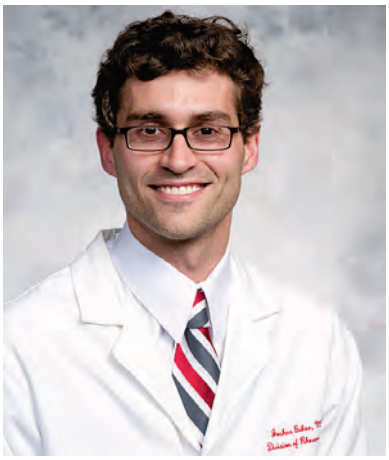
An analysis of data from two long-term clinical registries involving a total of 25,020 patients with rheumatoid arthritis and 62,484 person-years of follow-up revealed that severely obese individuals with RA had significantly higher Health Assessment Questionnaire or Multi-Dimensional-HAQ scores at enrollment, compared with overweight participants, even after adjusting for confounders such as age, sex, race, smoking, disease duration, and comorbidity.

The study, published online April 30 in Arthritis Care & Research, also showed that older, more obese individuals had greater increases in disability over time, particularly those with severe obesity. This was also seen in individuals with lower baseline Health Assessment Questionnaire scores, greater comorbidities, greater disease duration, and active smokers.

At the same time however, researchers saw a significantly larger increase in Health Assessment Questionnaire scores per year in individuals who had lost 5% or more of their weight since the age of 30. This association was evident after adjusting for body mass index at enrollment but was significantly more pronounced in individuals who were underweight. There was also a dose-dependent relationship between weight loss and subsequent worsening of disability.

Joshua F. Baker, MD, of the Philadelphia VA Medical Center and the University of Pennsylvania, and his coauthors wrote that, while cross-sectional studies have shown greater disability among obese patients with RA, the longitudinal effects of obesity hadn't been well characterized.

"Greater risks of worsening of disability in severely obese patients with RA are hypothesized to reflect the direct impact of adiposity and related comorbidities as opposed to more aggressive disease and higher disease activity," the authors wrote. "Furthermore, in this study, adjustment for CRP [C-reactive protein] and swollen joint counts over time did not attenuate associations between severe obesity and worsening disability in the VARA [Veterans Affairs RA] registry, suggesting associations are not easily explained by more severe inflammatory disease among obese individuals."


Dr. Baker

> "While intentional weight loss might be expected to have direct beneficial effects with regard to physical functioning and disability, these benefits are likely to be outweighed by the **more common scenario of unintentional weight loss in association with greater severity of chronic illness.**"

Commenting on the association between weight loss and worsening of disability, the authors said this may be a function of patients with more severe chronic illness experiencing weight loss.

"In RA, active inflammatory joint disease, chronic illness, comorbid disease, and worsening overall health can all contribute to weight loss," the authors said, pointing out that, while the reasons for the weight loss in the study were unknown, weight loss seen in similar observational studies was more commonly unintentional than intentional.

"Therefore, while intentional weight loss might be expected to have direct beneficial effects with regard to physical functioning and disability, these benefits are likely to be outweighed by the more common scenario of unintentional weight loss in association with greater severity of chronic illness," they wrote. Indeed, one of the two registries used in the study had previously found a strong correlation between weight loss and early risk of death.

They argued that this therefore still supported – rather than refuted – the accepted view that intentional weight loss was an important way to limit disability in people with rheumatoid arthritis.

One limitation of the study was the use of BMI to measure adiposity, which the authors suggested may not have been an accurate surrogate in people with chronic disease. They also acknowledged that measures of disease activity may be different between obese and nonobese patients, and adjusting for this was challenging.

Three authors acknowledged receiving grant awards from the U.S. Department of Veterans Affairs. No conflicts of interest were declared.

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SOURCE: Baker JF et al. Arthritis Care Res. 2018 Apr 30. doi: 10.1002/acr.23579.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4-week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

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

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

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

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 [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the HUMIRA 40 mg/0.8 mL Pen and 40 mg/0.8 mL, 20 mg/0.4 mL and 10 mg/0.2 mL prefilled syringe may contain natural rubber latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

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

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

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

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy.

No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

Anti-adalimumab antibodies were measured in clinical trials of subjects with moderate to severe HS with two assays (an original assay capable of detecting antibodies when serum adalimumab concentrations declined to < 2 mcg/mL and a new assay that is capable of detecting anti-adalimumab antibody titers in all subjects, independent of adalimumab concentration). Using the original assay, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%. Using the new titer-based assay, anti-adalimumab antibody titers were measurable in 61% of HS subjects treated with HUMIRA. Antibodies to adalimumab were associated with reduced serum adalimumab concentrations. In general, the extent of reduction in serum adalimumab concentrations is greater with increasing titers of antibodies to adalimumab. No apparent association between antibody development and safety was observed.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions, Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

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

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

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

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

Tuberculosis

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

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

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

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

Monitoring

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

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

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

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

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

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

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

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

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

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

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

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

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

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

CONGESTIVE HEART FAILURE

- Worsening and new onset congestive heart failure (CHF) has been reported with TNF blockers. Cases of worsening CHF have been observed with HUMIRA; exercise caution and monitor carefully.

AUTOIMMUNITY

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

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant. The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

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

References: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc. **2.** Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum.* 2004;50(5):1400-1411.

HUMIRA® adalimumab

For an adult patient with moderate to severe rheumatoid arthritis (RA)

"YOU SAVED THE LOTUS by helping to inhibit further joint damage and improving my physical function."

Susan R. **Yoga enthusiast with RA**

In a study of patients with established moderate to severe RA who had an inadequate response to methotrexate (MTX), those treated with HUMIRA + MTX vs placebo + MTX at 1 year had a:

- Mean change from baseline of 2.6 fewer Sharp score units[1]
- Greater mean improvement in HAQ-DI (-0.59 vs -0.25)[2]

HAQ-DI=Health Assessment Questionnaire Disability Index.

RA.HumiraConnect.com

Based on a real patient story from one of over 1 million patients treated for an FDA-approved indication, as of December 2017.* Individual results may vary. Model shown not an actual patient.

*Data on File, AbbVie Inc. IMS NPA and IMS NSP cumulative data as of Dec 2017.

INDICATIONS[1]

Rheumatoid Arthritis: HUMIRA is indicated, alone or in combination with methotrexate or other non-biologic DMARDs, for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

Psoriatic Arthritis: HUMIRA is indicated, alone or in combination with non-biologic DMARDs, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis.

Ankylosing Spondylitis: HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Juvenile Idiopathic Arthritis: HUMIRA is indicated, alone or in combination with methotrexate, for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

Uveitis: HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

SAFETY CONSIDERATIONS[1]

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

Malignancies: Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

Other Serious Adverse Reactions: Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

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

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

HUMIRA® adalimumab