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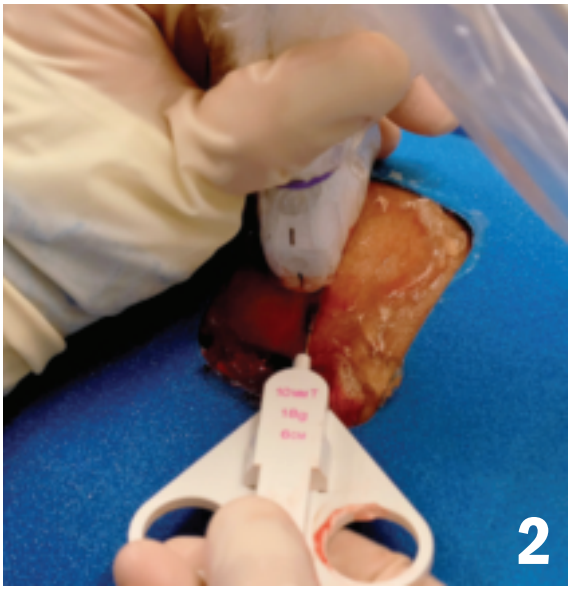

Synovial biopsy findings drive precision medicine for RA closer to the clinic

BY SHARON WORCESTER

Researchers are mining the synovium for potential treasure: robust markers to bring precision medicine to the rheumatoid arthritis arena. The signs, according to a number of recent reports, point toward a gold strike via synovial tissue biopsy (STB).

"I have no doubt about that – I am very confident that this concept of going straight to the tissue and using functional genomics will help us stratify our patients and will be a predictive model for patients with respect to therapy," Harris R. Perlman, PhD, the Mabel Greene Myers Professor of Medicine and chief of the division of rheumatology at Northwestern University, Chicago, said in an interview.

Dr. Perlman

Dr. Perlman is the principal investigator for the REASON (Rheumatoid Arthritis Synovial Tissue Network) study, and in a 2018 report on the network's efforts to train participants across the United States in ultrasound-guided joint biopsy techniques and to collect and analyze synovial tissue samples submitted by the six participating centers, he and his coinvestigators explained why a precision approach can't come soon enough.

"Currently, the standard of care for RA is to prescribe biologic therapy through a costly and time-consuming trial-and-error process. Therefore, the utility of a biomarker to identify how a patient will respond to a particular therapy cannot be overstated," they wrote (Arthritis Rheumatol. 2018 Jun;70[6]:841-54).

Since that REASON report was published, efforts by the investigators and others, such as those involved with the Accelerating Medicines Partnership (AMP) in RA and Lupus Network, to identify such biomarkers have continued to yield encouraging results.

Dr. Pitzalis

In fact, data from the phase 4 R4-RA (Response, Relapse, and Resistance to Rituximab Therapy in Patients With RA) trial – the first randomized, controlled, biopsy-driven trial in RA – were reported in November 2019 at the annual meeting of the American College of Rheumatology. R4-RA demonstrated that patients with B cell–poor RA identified on STB responded better to tocilizumab (Actemra) than to rituximab (Rituxan), whereas those with B cell–rich RA on STB did not, Constantino Pitzalis, MD, head of the Centre for Experimental Medicine & Rheumatology at Queen Mary University of London said, noting that the findings could have "massive implications" for RA management and outcomes.

Numerous treatments exist for RA, but methods for determining which to use for a given patient are sorely lacking and the field of rheumatology lags behind others, like oncology, in bringing individualized medicine to the clinic, he explained.

Reasons to use STB

Despite extensive efforts, blood testing has failed to yield markers sufficient for guiding RA treatment, and although the synovium has long been considered a potentially better source of information to guide treatment given the damage it sustains from RA, biopsies have generally been accessible only during arthroscopic or joint replacement surgery in patients with severe disease, which doesn't reflect the population of patients who could benefit from early intervention, Dr. Perlman and colleagues explained in their 2018 report.

Musculoskeletal ultrasound (US) technology, however, has advanced dramatically over the past decade, is available and used by rheumatologists in clinical practice, and has brought US-guided joint biopsies to the forefront of research. Such techniques have been used in Europe for years, and as a result, an extensive catalog of

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literature supports the safety, feasibility, and tolerability of the approach.

A recent study in Portugal by Romao et al., for example, showed "remarkably high" patient tolerability (70%) with 64 US-guided procedures, including 52 in clinical practice and 12 for research purposes. No major adverse events occurred, and biopsy usefulness was high, with 37% having a direct diagnostic impact and with 100% and 95% positive- and negative-predictive values for infection. Further, synovial tissues were retrieved in 88% of biopsies and a median of 75% of samples were gradable (Arthritis Care Res. 2019 Aug 17. doi: 10.1002/acr.24050).

A 2018 study of 524 synovial biopsies, including 402 performed using US-guided needle biopsy, performed at five centers across Europe similarly demonstrated safety and patient tolerability (RMD Open. 2018;4[2]:e000799. doi: 10.1136/mdopen-2018-000799).

Building on the work in Europe, investigators at Northwestern launched the REASON study, assembling a consortium of academic rheumatology groups across the United States, training participants in minimally invasive US-guided joint biopsy techniques, and collecting and analyzing synovial tissue samples submitted by the participating centers.

Laura B. Hughes, MD, a professor at the University of Alabama at Birmingham and an investigator in both the REASON study and AMP, said in an interview that her experience with patients is similar.

"It has been very, very well tolerated," she said of the biopsy procedure used in the course of the studies – and that's despite the time and commitment required, she added, explaining that 12 samples, each requiring a separate injection, are obtained over a 30- to 45-minute visit.

"We've had no problems, no complications," she said, also noting the importance of careful patient selection.

Patients are altruistic; they want to be a part of moving things forward and helping other patients, and they have been more than willing to participate, both she and Dr. Perlman noted.

Courtesy Dr. Arthur Mandelin/Feinberg University School of Medicine

A synovial tissue biopsy procedure is shown in progress.

In fact, the REASON study investigators reported that performance of STB by rheumatologists in the United States is feasible and generates high-quality samples.

Further, the transcriptional profiles of isolated RA synovial macrophages identified from samples submitted by Dr. Hughes and others in the network characterized subpopulations of patients and identified six novel transcriptional modules associated with disease activity and therapy, underscoring the potential for precision medicine in RA.

"We posit that transcriptional signatures in macrophages ... will predict responsiveness to specific nonbiologic and/or biologic therapies," they wrote, adding that future studies will "entail collection of synovial biopsy specimens from a larger cohort longitudinally, prior to, and following therapy."

The ongoing National Institutes of Health–funded AMP Network research is also using synovial biopsies, but more for identification of molecular pathways with a focus on potential drug development.

A 2019 report from the AMP investigators described their integrated use of single-cell transcriptomics and mass cytometry to reveal cell states expanded in RA synovia and the mapping of inflammatory mediators to their source cell populations, which may be key mediators of RA pathogenesis.

"We observed upregulation of chemokines (CXCL8, CXCL9, and CXCL13), cytokines (IFNG and IL15), and surface receptors (PDGFRB and SMAMF7) in distinct immune and stromal cell populations, suggesting potential novel targets," they wrote (Nat Immunol. 2019 Jul;20[7]:928-42).

Next steps

These reports, along with the thousands of papers published over the past few decades describing phenotypic and functional abnormalities in synovial tissue obtained from RA patients undergoing joint replacement surgery or, more recently, via STB early in the course of disease, have provided a wealth of information, Helen Michelle McGettrick, MD, noted in an editorial addressing the potential of STB analysis for "unlocking the hidden secrets to personalized medicine."

The question, however, is whether they have moved the field closer to "translating this discovery science into new biomarkers or drugs to improve diagnosis or prognosis," she wrote (Arthritis Res Ther. 2019;21[90]. doi:

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10.1186/s13075-019-1871-5).

"Three sides of our square are in place: clinical expertise, technology, and patient willingness," she said, arguing that the fourth side is "standardization in the handling, evaluation, and interpretation of STB."

In fact, her editorial focused on a joint consensus of the European League Against Rheumatism Synovitis Study Group and the OMERACT Synovial Tissue Biopsy Group (Arthritis Res Ther. 2018;20[265]. doi: 10.1186/s13075-018-1762-1).

Dr. Hughes

The groups, based on member survey responses, proposed a "consensual set of analysis items" to be used for synovial biopsies in clinical practice and translational research, including matters such as biopsy sampling, histologic criteria, and biopsy interpretation. Their work, according to Dr. McGettrick and the authors themselves, marked a step forward, but provided only a foundation for a standardization framework.

One particular area of synovial research that has received recent attention and which illustrates the need for standardization involves the role of synovial B cells in RA. The R4-RA researchers, in conjunction with the Pathobiology of Early Arthritis Cohort, are working to better define the relationship of synovial B cells to clinical RA phenotypes at various disease stages and drug exposures as a potential source of predictive and prognostic biomarkers, and in an article accepted for publication in Arthritis & Rheumatology, they describe a "robust semiquantitative histological B cell score that closely replicates the quantification of B cells by digital or molecular analyses."

In their study of 329 patients, they demonstrated an ongoing B cell–rich synovitis more prevalent in patients with established RA who had inadequate response to tumor necrosis factor inhibitor therapy than in those with early RA (47.4% vs. 35%), but which does not appear to be captured by standard clinimetric assessment (Arthritis Rheumatol. 2019 Nov 29. doi: 10.1002/art.41184).

"Overall, our study confirms the relevance of synovial B cells in RA and suggests that the classification of patients into B cell–rich/–poor can contribute to patient stratification," they concluded.

In a related editorial, Dana E. Orange, MD, and Laura T. Donlin, PhD, of the Hospital for Special Surgery, New York, note that previously discrepant findings with respect to the value of B-cell infiltrate scores for predicting RA treatment response may relate to the lack of a standardized scoring system (Arthritis Rheumatol. 2019 Nov 29. doi: 10.1002/art.41185).

Together, these emerging findings are "advancing our understanding of the transcriptional and cellular characteristics of the synovium in RA," they wrote, concluding that incorporation of synovial assessments into clinical management of patients is "the next step in empowering clinicians to apply advances in molecular immunology to better tailor treatment decisions."

Indeed, an important goal is empowering rheumatologists to become adept in obtaining synovial biopsies in clinical practice, much like gastroenterologists collect tissue for biopsy via colonoscopy, Dr. Pitzalis said in an interview following his R4-RA presentation at the ACR meeting.

Dr. Hughes predicts that a subset will embrace the concept, but not all rheumatologists are interested and not all use musculoskeletal US in their practice.

"It requires a lot of training, there is a credentialing exam, and it's not necessary for practicing rheumatology, but there is a lot of growth," she said, noting that training is being promoted through the ACR and other organizations, and Europeans who are well-versed in US-guided STB have served as mentors. "It's been a nice collaboration, and I think it's just going to push the field forward ... it really is exciting – I think synovial biopsies will yield a lot of information and really, hopefully, help us target therapy and find new therapeutic targets that we haven't even thought of."

However, Dr. Pitzalis stressed that there remains much work to do.

"It's important to understand this is early data and will require validation in larger and target-driven and biopsy-driven treatment clinical trials," he said of the R4-RA findings.

"It's important to understand this is early data and will require validation in larger and target-driven and biopsy-driven treatment clinical trials."

Those efforts are underway; the REASON study, for example, is moving forward, having recently been awarded a National Institutes of Health Research Project Grant, Dr. Perlman said, explaining that the latest goal is to determine whether the transcription modules the investigators have identified to date can be predictive of treatment response.

He expects to report outcomes at ACR 2020, and noted that preliminary findings suggest that "we can tell, by 4 weeks, which patients will respond or not."

Dr. Pitzalis and his colleagues are also working on their "next set of trials," which are using biopsies for treatment allocation (B cell–poor patients get one drug, B cell–rich patients, another, for example), and he, too said he expects to have additional data to present at ACR 2020.

"If we are to demonstrate clinical utility, I think rheumatology will be ready to implement this methodology in clinical practice," he said.

The authors interviewed for this article reported having no relevant financial disclosures.

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Ready for PRIME time? Newly identified cells predict RA flares

BY NEIL OSTERWEIL
FROM THE NEW ENGLAND JOURNAL OF MEDICINE

A newly identified circulating cell type may be a reliable marker for impending RA flares. The discovery and description of the cells, which bear a "striking" similarity to synovial fibroblasts, provide important clues to the origins of RA and progressive joint inflammation, investigators say.

By studying longitudinally collected blood samples from four patients with RA over 4 years, Dana E. Orange, MD, of the Hospital for Special Surgery, New York, and colleagues identified a pattern of B-cell activation and expansion of circulating cells that are negative for CD45 and CD31 expression, and positive for PDPN, dubbed preinflammatory mesenchymal or "PRIME" cells.


Dr. Orange

Expansion of PRIME cells in circulation increased dramatically in the weeks leading up to a flare and decreased during a flare, suggesting the possibility of a serum assay for predicting flares and allowing for early intervention to ameliorate or prevent disabling consequences, the investigators wrote in a study published in the New England Journal of Medicine.

"Our hope is that this will be a diagnostic in the future, but we need to study it in more patients to see how it will perform," Dr. Orange said in an interview, adding that the cells, if shown to be pathogenic, could also be targets for new therapeutic strategies.

RNA sequencing

Dr. Orange and colleagues discovered the PRIME cells through a novel clinical and technical protocol involving home collection of blood by patients and longitudinal RNA sequencing to study gene expression profiles during times of both disease quiescence and flares, and noticed a distinct pattern of PRIME cell expansion, depletion, and gene expression.


Suze777/Getty Images

"Looking at their gene expression profiles, they overlapped with fibroblasts that reside in inflamed rheumatoid arthritis synovium, and in an animal model those types of fibroblasts were important for allowing entry of inflammatory infiltrates around the joint," she said.

PRIME cells may be a precursor of synovial fibroblasts, which have been implicated by some researchers in the spread of RA between joints, Dr. Orange added.

Homework for patients

The investigators began by enrolling four patients, followed for 1-4 years, who met 2010 American College of Rheumatology–European League Against Rheumatism criteria and who were seropositive for anti–cyclic citrullinated peptide antibodies.

They assessed disease activity from patient homes weekly or during escalation of flares up to four times daily, with the Routine Assessment of Patient Index Data 3 (RAPID3) questionnaire, as well as monthly clinic visits. At clinic visits during flares, disease activity was assessed using both the RAPID3 and 28-joint Disease Activity Score.

The patients performed fingerstick blood collection and mailed the samples overnight each week to Rockefeller University, where RNA was extracted and sequenced. The investigators identified gene transcripts that were differentially expressed in blood prior to flares, and compared them with data profiles derived from synovial single-cell RNA sequencing.

To validate the findings, the researchers used flow cytometry and sorted blood-cell RNA sequencing of samples from an additional 19 patients with RA.

They found that a total of 2,613 genes were differentially expressed during a flare, compared with baseline, and that expression of 1,437 of these genes was increased during a flare, with the remaining 1,176 decreased during flares.

Possible storm predictors

Focusing on two flare-antecedent clusters of genes, they identified one cluster of transcripts that increased 2 weeks before a flare, enriched with genes coding for developmental pathways for naive B cells (that is, not yet exposed to antigens) and leukocytes.

The second cluster included gene transcripts that increased during the week before a flare, then decreased over the duration of the flare. Genes in this cluster were enriched for pathways that were unexpected in typical blood specimens, including genes involved in cartilage morphogenesis, endochondral bone growth, and extracellular matrix organization. The gene activity suggested the presence of a mesenchymal cell, they wrote.

The RNA expression profiles of these newly identified PRIME cells were very similar to those of synovial fibroblasts, and the investigators specu-

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lated that PRIME cells may be synovial fibroblast precursors.

They proposed a model of RA exacerbation in which PRIME cells become activated by B cells in the weeks immediately preceding a flare, and then migrate out of blood into the synovium.

The investigators are currently investigating "how reproducible this signature is in different flares in patients on different types of background therapy, and then we're very interested in looking at the upstream triggers of the B cell and the PRIME cell," Dr. Orange said.

"One of the reasons this is very exciting is that there are these signatures that can be found when patients are clearly asymptomatic but about to flare, and if we can intervene at that time, then the patients won't have to live through a flare; they won't have to have that experience," she said.

Pros and cons

In an editorial accompanying the study, Ellen M. Gravallese, MD, from Brigham and Women's Hospital in Boston and William H. Robinson, MD, PhD, from Stanford (Calif.) University and the Veterans Affairs Palo Alto (Calif.) Health Care System wrote that the study demonstrates an important method for identifying genetic contributions to many different types of disease.

"Orange and colleagues show that intensively collected longitudinal data from a small sample of patients can be used to identify dysregulated transcriptional signatures that are not recognized by classical cross-sectional studies. This study illustrates the exciting potential of longitudinal genomics to identify key antecedents of disease flares in an approach that may be applicable to the investigation of pathogenic and protective immune responses in a wide range of human diseases," they wrote.

Rheumatology researcher Christopher D. Buckley, MBBS, DPhil, from the University of Birmingham (England), who was not involved in the study, said that the use of blood samples is both a strength and a weakness of the study.

"Blood is much easier to get than synovial tissue, but synovial tissue is important. If I'm trying to look at the blood and trying to make an inference about what's going on in the synovium, if I don't look at the synovium I don't know what the link between the blood and synovium is," he said in an interview.

On the plus side, "the big advantage about looking at blood is that you do multiple time points, which is really cool," he said.

Dr. Buckley is a coauthor of a recent paper in Nature Medicine – published after the study by Dr. Orange and colleagues was accepted by the New England Journal of Medicine – showing that a population of macrophages in synovium was highly predictive of remission in patients with RA, and that therapeutic modulation of these macrophages has the potential as a treatment strategy for RA (Nat Med. 2020 Jun 29. doi: 10.1038/s41591-020-0939-8).

Dr. Buckley

"We are very keen to understand the cellular basis of disease. We're very good at understanding genes, but genes have to work in cells, and cells make organs, so the cells are critical," he said.

The paper adds fuel to a controversy that has been raging among rheumatology researchers for more than a decade: the "flying fibroblast" hypothesis, which suggests that fibroblasts can migrate from one joint to another, hence spreading the disease in a manner akin to cancer metastases.

"It's been quite controversial whether these cells like fibroblasts can exist in the blood, or whether they're found in sufficient number in the blood," Dr. Buckley said. "The fact that they have identified these PRIME cells is fascinating, because that's going to cause us to go back and reinvestigate the whole flying fibroblast story."

His colleague John Isaacs, MBBS, PhD, from Newcastle University, Newcastle Upon Tyne, England is principal investigator for the BIO-FLARE study, in which participants with RA stop taking their disease-modifying antirheumatic drugs under close supervision of researchers. The investigators then study the patients looking for flare signals as well as the biology of flares themselves.

"As it happens, our protocols would not pick up this particular cell, because we have not been focusing on the stroma, at least not in peripheral blood. We've all been looking at synovium as part of BIO-FLARE," he said in an interview. "We will be looking for this cell now that we have seen this research, and certainly we would want to replicate."

He agreed with Dr. Buckley's observation that the PRIME cell data may revive the flying fibroblast hypothesis. "This is a great paper in a top clinical journal. What isn't there is mechanism. That's the thing we're all going to want to understand now: Where do the cells come from, how do they actually trigger flares, and how do they go down as flare starts?"

Dr. Isaacs

Both Dr. Buckley and Dr. Isaacs agreed that the study findings point to important new avenues of research, but also noted that the study was small, involving a total of only 23 patients, and that replication of the findings and elucidation of the mechanism of PRIME cell generation and disposition will be required.

The study was supported by grants from the National Institutes of Health, Simons Foundation, Robertson Foundation, Rheumatology Research Foundation, Bernard and Irene Schwartz Foundation, the Iris and Junming Le Foundation, and Rockefeller University. Dr. Orange disclosed a provisional patent for the discovery of the PRIME cells. Dr. Buckley and Dr. Isaacs reported no relevant conflicts of interest.

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SOURCE: Orange DE et al. N Engl J Med. 2020 Jul 15. doi: 10.1056/NEJMoa2004114.

In rheumatology, biosimilars are flatlining. Why?

BY KARI OAKES
FROM ARTHRITIS & RHEUMATOLOGY

Although biosimilar versions of tumor necrosis factor inhibitors (TNFis) have been available to U.S. rheumatologists and their patients for over 3 years, uptake has thus far been slow.

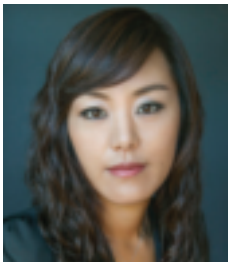
In an analysis of data from a large commercial payer, the two available biosimilars for infliximab (Remicade) accounted for less than 1% of TNFi prescribing since the first biosimilar to infliximab was approved in 2016.

The study, published in Arthritis & Rheumatology, involved a total of 1.1 million TNFi prescriptions or infusions received by 95,906 patients from 2016 to 2019. Investigators found that uptake of biosimilar infliximab was essentially flat, standing at 0.1% of prescribing in the second quarter of 2017, and topping out at 0.9% in the first quarter of 2019. For branded infliximab, prescribing was also stable, but accounted for about 20% of overall biologic dispensing in each quarter of the period studied.

There are currently two biosimilar medications to the originator infliximab, which is one of five originator biologics available to treat rheumatic diseases in the United States: infliximab-dyyb (Inflectra) and infliximab-abda (Renflexis). The former was approved in 2016 and the latter in 2017, said study author Seoyoung C. Kim, MD, ScD, of the division of pharmacoepidemiology and pharmacoeconomics, Brigham and Women's Hospital, Boston, and her coauthors.

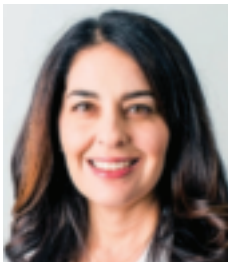
"Our paper reports a disappointingly low uptake of biosimilar infliximab since the first quarter of 2017 using claims data from a large private health plan. The main and maybe the only reason to consider using a biosimilar is cost saving," said Dr. Kim in an interview. "Our results suggest that current modest cost savings from infliximab biosimilars in the U.S. are not sufficient to promote their widespread use."

In the payer database study conducted by Dr. Kim and colleagues, the insurer paid similar mean amounts per patient per quarter for originator and biosimilar infliximab in mid-2017 ($8,322 versus $8,656). By the end of 2018, a gap appeared, with the insurer paying a mean quarterly per-patient sum of $8,111 for biosimilar infliximab compared with $9,535 for the branded biologic.


Dr. Kim

Unrealized potential for cost savings

"The lack of market penetration and very modest price reductions for biosimilars have left policymakers, payers, physicians, and the public frustrated, particularly because sales in Europe continue to rapidly expand and robust cost-savings have materialized," wrote Jinoos Yazdany, MD, MPH, in an editorial accompanying the study.


Dr. Yazdany

Dr. Yazdany, professor and chief of the division of rheumatology at the University of California, San Francisco, noted that increased spending on biologics in the United States – which increased by 50% from 2014 to 2018 – has been driven by rising prices as well as increased uptake of biologic therapies.

At least in part, Europe has been able to reap cost savings where the United States hasn't because fundamental differences in health care reimbursement can ease sweeping biosimilar adoption, Dr. Yazdany noted. "Countries like Denmark and Sweden, using the negotiating and purchasing power of their single-payer systems have instituted a winner-takes-all bidding system," with Denmark seeing cost savings of up to two-thirds when bidding was combined with mandatory switching, she said.

The continued market dominance of originator infliximab means that savings from biosimilars have thus far amounted to about $91 million, far short of the $1 billion that the Congressional Budget Office had projected for this date, Dr. Yazdany said.

One problem in the adoption of biosimilars by U.S. rheumatologists may have been uneven marketing and pricing across different types of practice, Colin C. Edgerton, MD, a rheumatologist at Low Country Rheumatology in South Carolina and chair of the American College of Rheumatology's Committee on Rheumatologic Care, said in an interview.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"Rheumatologists have generally developed comfort with biosimilars, although this is not universal. The core message, that all biologics vary and that this is OK, is getting out. In general, rheumatologists also understand the problem with high drug prices and the threat to patient access," Dr. Edgerton said. But "the early marketing and pricing focus for biosimilars seemed to be on hospitals and facilities, and this did not work effectively for community rheumatologists, where the majority of care is delivered. We have been pleased to see a manufacturer pivot toward community rheumatology where additional efforts need to be made to bend the curve on biosimilar adoption. It is critical for practices with experience using biosimilars to educate peers, and this is where networks of practicing rheumatologists are important."

Contributors to lack of biosimilar use

In Dr. Yazdany's editorial, she cited four structural factors impeding biosimilar uptake and downstream savings.

First, she cites ongoing actions by pharmaceutical companies, which create a "patent thicket" that has the effect of fencing off originator biologics from biosimilars long beyond the original 12-year exclusivity period. Supporting the notion that "patent thickets" are a common strategy, Dr. Yazdany noted that almost half of the patent applications that AbbVie has filed for adalimumab (Humira) have come in after the original exclusivity period expired in 2014. Humira's price has risen 18% yearly during this period.

The complicated role played by pharmacy benefit managers (PBMs) is another factor in slow adoption, said Dr. Yazdany: When manufacturers offer rebates to PBMs, the price of the originator biologic may be less than its biosimilar. Further, manufacturers may sign multiyear rebate agreements just before a biosimilar launch; PBMs are also sometimes threatened with the withdrawal of rebates if they offer biosimilars, she noted.

Third, prescriber inertia may also be at play, Dr. Yazdany noted, not least because patients often see little difference in out-of-pocket costs when they make the switch to a biosimilar – PBM rebates are not necessarily passed on to patients. Payers may not reimburse a biosimilar, or formularies can be built without them, influencing prescribing, and there's usually no reimbursement incentive for biosimilar prescribing in the nonpublic sector, she said. To the contrary, infusing a drug with a higher price often means higher reimbursement for the administering clinician, since commercial insurance reimbursement is often calculated as a percent of the charge for the drug.


Dr. Edgerton

Dr. Edgerton said that rheumatologists can affect the use of biosimilars by talking with patients about the "nocebo effect" relating to biosimilars. "This is a phenomenon in which patients are thought to experience worsening symptoms associated with negative beliefs about biosimilars. There has been a study in Arthritis Care & Research addressing this concern. The authors found that positive framing of biosimilars led to more participants being willing to switch than negative framing. This suggests that clinicians have an important role in informing patients about biosimilars, and addressing hesitancy."

Finally, Dr. Yazdany pointed out that, for a pharmaceutical company pursuing biosimilar approval, the regulatory pathway itself can provide its own set of complications and confusion. Biosimilars are not exact molecular replicas of the originator biologic, and these differences can change efficacy and immunogenicity, and also affect stability. Hence, a company wishing to market a biosimilar has to show the Food and Drug Administration that safety and efficacy aren't affected by a switch to biosimilar from an originator biologic. Extrapolation from one indication to another can be made – with scientific justification.

The FDA is currently using postmarketing pharmacovigilance to monitor biosimilar performance in the real world, and a recent systematic review "should provide some reassurance," wrote Dr. Yazdany, citing the study, which looked at 14,000 patients who had a total of 14 disease indications for biosimilar use. The 90-article review largely found no differences in safety, efficacy, or immunogenicity between originators and their biosimilars. Dr. Yazdany recommended greater openness to incorporating the European experience in the FDA's ongoing reassessment.

A further way forward can come through tackling the patent thicket with the proposed bipartisan Biologic Patent Transparency Act, which would require publication of biologic patents in a one-stop publicly searchable database. Going further with legislation to address anticompetitive activity by pharmaceutical companies could shorten the runway to biosimilar launching considerably, she noted.

The complicated landscape of PBMs and rebates affects many sectors of health care, and new policy efforts are needed here as well, she said. Reimbursement strategies – and much-needed continuing medical education – can both ease prescriber unfamiliarity with biosimilars and provide incentives for their use, she concluded.

Dr. Yazdany is supported by the Alice Betts Endowed Chair in Arthritis Research, the Russel/Engleman Research Center at the University of California, San Francisco, and the National Institutes of Health. She has received independent research grants from Pfizer and Genentech and research consulting fees from Eli Lilly and AstraZeneca.

Dr. Kim's study was supported by the division of pharmacoepidemiology and pharmacoeconomics, department of medicine, Brigham and Women's Hospital, and Arnold Ventures. Dr. Kim has received research grants to Brigham and Women's Hospital from Pfizer, AbbVie, Bristol-Myers Squibb, and Roche.

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SOURCES: Kim SC et al. Arthritis Rheumatol. 2020 Jan 13. doi: 10.1002/art.41201; Yazdany J. Arthritis Rheumatol. 2020 Jan 10. doi: 10.1002/art.41203.

Financial incentives differentially affect the adoption of biosimilars across practice settings

BY ERIK GREB
FROM ARTHRITIS & RHEUMATOLOGY

The adoption of the infused biosimilar infliximab therapies Inflectra and Renflexis was slower at an academic medical center than at a neighboring Veterans Affairs Medical Center (VAMC) during the same time period in 2015-2019, according to an analysis published in Arthritis and Rheumatology.

The use of the biosimilars also was associated with cost savings at the VAMC, but not at the academic medical center, which illustrates that insufficient financial incentives can delay the adoption of biosimilars and the health care system's realization of cost savings, according to the authors.

Medicare, which is not allowed to negotiate drug prices, is one of the largest payers for infused therapies. Medicare reimbursement for infused therapies is based on the latter's average selling price (ASP) during the previous quarter. Institutions may negotiate purchase prices with drug manufacturers and receive Medicare reimbursement. Biosimilars generally have lower ASPs than their corresponding reference therapies, and biosimilar manufacturers may have less room to negotiate prices than reference therapy manufacturers. Consequently, a given institution might have a greater incentive to use reference products than to use biosimilars.

Pharmacy data examined

The VA negotiates drug prices for all of its medical centers and has mandated that clinicians prefer biosimilars to their corresponding reference therapies, so Joshua F. Baker, MD, of the University of Pennsylvania and the Corporal Michael J. Crescenz VAMC, both in Philadelphia, and his colleagues hypothesized that the adoption of biosimilars had proceeded more quickly at a VAMC than at a nearby academic medical center.

The investigators examined pharmacy data from the University of Pennsylvania Health System (UPHS) electronic medical record and the Corporal Michael J. Crescenz VAMC to compare the frequency of prescribing biosimilars at these sites between Jan. 1, 2015, and May 31, 2019. Dr. Baker and his associates focused specifically on reference infliximab (Remicade) and the reference noninfusion therapies filgrastim (Neupogen) and pegfilgrastim (Neulasta) and on biosimilars of these therapies (infliximab-dyyb [Inflectra], infliximab-abda [Renflexis], filgrastim-sndz [Zarxio], and pegfilgrastim-jmdb [Fulphila]).


Dr. Baker

Because Medicare was the predominant payer, the researchers estimated reimbursement for reference and biosimilar infliximabs according to the Medicare Part B reimbursement policy. They defined an institution's incentive to use a given therapy as the difference between the reimbursement and acquisition cost for that therapy. Dr. Baker and colleagues compared the incentives for UPHS with those for the VAMC.

VAMC saved 81% of reference product cost

The researchers identified 15,761 infusions of infliximab at UPHS and 446 at the VAMC during the study period. The proportion of infusions that used the reference product was 99% at UPHS and 62% at the VAMC. ASPs for biosimilar infliximab have been consistently lower than those for the reference product since July 2017. In December 2017, the VAMC switched to the biosimilar infliximab.

Institutional incentives based on Medicare Part B reimbursement and acquisitions costs for reference and biosimilar infliximab have been similar since 2018. In 2019, the institutional incentive favored the reference product by $49-$64 per 100-mg vial. But at the VAMC, the cost per 100-mg vial was $623.48 for the reference product and $115.58 for the biosimilar Renflexis. Purchasing the biosimilar thus yielded a savings of 81%. The current costs for the therapies are $546 and $116, respectively.

In addition, Dr. Baker and colleagues identified 46,683 orders for filgrastim or pegfilgrastim at UPHS. Approximately 90% of the orders were for either of the two reference products despite the ASP of biosimilar filgrastim being approximately 40% lower than that of its reference product. At the VAMC, about 88% of orders were for the reference products. Biosimilars became available in 2016. UPHS began using them at a modest rate, but their adoption was greater at the VAMC, which designated them as preferred products.

Tendering and mandating a nationwide policy on the use of biosimilars have resulted in financial savings for the VAMC, wrote Dr. Baker and colleagues. "These data suggest that, with current Medicare Part B reimbursement policy, the absence of financial incentives to encourage use of infliximab biosimilars has resulted in slower uptake of biosimilar use at institutions outside of the VA system. The implications of this are a slower reduction in costs to the health care system, since decreases in ASP over time are predicated on negotiations at the institutional level, which have been gradual and stepwise. ...

"Although some of our results may not be applicable to other geographical regions of the U.S., the comparison of two affiliated institutions in geographical proximity and with shared health care providers is a strength," they continued. "Our findings should be replicated using national VAMC data or data from other health care systems."

The researchers said that their findings may not apply to noninfused therapies, which are not covered under

Continued on following page ▸

No link seen between methotrexate and interstitial lung disease in two studies

BY SUSAN LONDON
FROM THE EULAR 2020 E-CONGRESS

Patients with RA have an elevated risk of interstitial lung disease (ILD), but methotrexate does not accentuate that risk and may in fact be protective, new data show. These were among key findings of a pair of studies reported at the annual European Congress of Rheumatology, held online this year for COVID-19.

Although a guideline-recommended cornerstone in the management of RA, methotrexate has been associated with both hypersensitivity pneumonitis and diffuse lung disease. However, its involvement in the development of ILD among patients with RA is unclear.

A Danish study of more than 30,000 RA patients reported at the congress found that their risk of ILD was about three to five times that of the general population. However, risk did not differ significantly whether they had filled a methotrexate prescription or not.

In addition, a multinational case-control study of more than 1,000 RA patients also reported at the congress found that, compared with never-users of methotrexate, ever-users actually had a 59% lower likelihood of developing ILD.

However, both studies were limited by their retrospective design, Elizabeth R. Volkmann, MD, codirector of the connective tissue disease–related interstitial lung disease program at the University of California, Los Angeles, cautioned in an interview. Hence, there was likely systematic bias and confounding.

"I would interpret the conclusions of both studies with caution," she maintained. "To understand how a particular intervention, such as methotrexate use, affects the outcome of ILD development, a prospective design is needed, which adequately adjusts for known ILD risk factors, such as male sex and smoking."

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Medicare Part B, and they did not directly study the impact of pharmacy benefit managers. However, they noted that their data on filgrastim and pegfilgrastim support the hypothesis that pharmacy benefit managers receive "incentives that continue to promote the use of reference products that have higher manufacturer's list prices, which likely will limit the uptake of both infused and injectable biosimilar therapies over time." They said that "this finding has important implications for when noninfused biosimilars (e.g., etanercept and adalimumab) are eventually introduced to the U.S. market."

European governments incentivize use of biosimilars

Government and institutional incentives have increased the adoption of biosimilars in Europe, wrote Guro Lovik Goll, MD, and Tore Kristian Kvien, MD, of the department of rheumatology at Diakonhjemmet Hospital in Oslo, in an accompanying editorial (Arthritis Rheumatol. 2020 Apr 9. doi: 10.1002/ART.41280). Norway and Denmark have annual national tender systems in which biosimilars and reference products compete. The price of infliximab biosimilar was 39% lower than the reference product in 2014 and 69% lower in 2015. "Competition has caused dramatically lower prices both for biosimilars and also for the originator drugs competing with them," wrote the authors.


Dr. Goll


Dr. Kvien

In 2015, the government of Denmark mandated that patients on infliximab be switched to a biosimilar, and patients in Norway also have been switched to biosimilars. The use of etanercept in Norway increased by 40% from 2016 to 2019, and the use of infliximab has increased by more than threefold since 2015. "In Norway, the consequence of competition, national tenders, and availability of biosimilars have led to better access to therapy for more people in need of biologic drugs, while at the same time showing a total cost reduction of biologics for use in rheumatology, gastroenterology, and dermatology," wrote the authors.

Health care costs $10,000 per capita in the United States, compared with $5,300 for other wealthy countries in the Organization for Economic Cooperation and Development. Low life expectancy and high infant mortality in the U.S. indicate that high costs are not associated with better outcomes. "As Americans seem to lose out on the cost-cutting potential of biosimilars, this missed opportunity is set to get even more expensive," the authors concluded.

The U.S. Department of Veterans Affairs, the National Institutes of Health, and the American Diabetes Association contributed funding for the study. Dr. Baker reported receiving consulting fees from Bristol-Myers Squibb and Gilead, and another author reported receiving research support paid to his institution by Pfizer and UCB, as well as receiving consulting fees from nine pharmaceutical companies. Dr. Goll and Dr. Kvien both reported receiving fees for speaking and/or consulting from numerous pharmaceutical companies, including Pfizer.

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SOURCES: Baker JF et al. Arthritis Rheumatol. 2020 Apr 6. doi: 10.1002/art.41277.

Dr. Elizabeth R. Volkmann

Continued from previous page

As to whether the new findings are practice changing and how they might affect patient counseling, "the answers to these questions are not straightforward and depend on other patient-related factors," according to Dr. Volkmann.

Danish nationwide study

René Cordtz, MD, a clinical assistant at the Center for Rheumatology and Spine Diseases, Rigshospitalet-Gentofte, Copenhagen, and colleagues conducted a nationwide population-based cohort study using registry data from 1997 to 2015 to assess lung disease among patients with RA by prescriptions filled.

Results based on 30,512 RA patients showed that, compared with peers filling no methotrexate prescriptions, patients filling at least one did not have a significantly elevated risk of ILD at either 1 year of follow-up (hazard ratio, 1.03) or 5 years of follow-up (HR, 1.00). (Findings were similar for sulfasalazine, with respective nonsignificant HRs of 0.88 and 1.14.)

In addition, patients with RA had a similarly sharply elevated 5-year risk of ILD relative to the general population regardless of whether they had filled neither methotrexate nor sulfasalazine prescriptions (standardized incidence ratio, 3.38) or had filled prescriptions for methotrexate only (SIR, 3.63), sulfasalazine only (SIR, 4.12), or both (SIR, 5.45).

"RA patients have an increased risk of ILD, compared to the general population, which was not surprising, but very importantly, that risk was not further exacerbated in those treated with methotrexate," Dr. Cordtz concluded. "We do acknowledge that purchasing your medicine is different from taking your medicine, which is why we found it extra reassuring that, when requiring at least two methotrexate prescriptions to be considered exposed, it did not change our results."

Multinational study

Pierre-Antoine Juge, MD, a rheumatologist at Bichat-Claude Bernard Hospital, Paris, and colleagues performed a case-control study among 482 RA patients with ILD and 741 RA patients without ILD in three cohorts: a French discovery cohort, a multinational (Brazilian, Italian, Mexican, United Kingdom, and United States) replication cohort, and a combined cohort. Those with methotrexate hypersensitivity pneumonitis were excluded.

Results showed that, relative to peers without ILD, patients with ILD had a lower prevalence of ever having used methotrexate and had received a lower cumulative methotrexate dose, findings that were consistent across all three cohorts.

Methotrexate ever-use was associated with a significantly lower adjusted likelihood of ILD in the discovery cohort (odds ratio, 0.46), the replication cohort (OR, 0.38), and the combined cohort (OR, 0.41). Furthermore, ever-users were less commonly represented among patients with ILD regardless of chest high-resolution CT pattern (usual interstitial pneumonia pattern vs. not).

Dr. Pierre-Antoine Juge

Finally, methotrexate use appeared to delay the adjusted time to onset of ILD by 3.5 years in the discovery cohort ($P = .001$), by 3.2 years in the replication cohort ($P < .0001$), and by 3.5 years in the combined cohort ($P < .0001$).

"Outside of methotrexate hypersensitivity pneumonitis, methotrexate was not a risk factor for RA-associated ILD in our study. We observed an inverse relationship that was similar whatever the high-resolution CT pattern," Dr. Juge commented. "But this possible protective effect should be confirmed through a dedicated prospective, randomized, controlled trial."

"Methotrexate should not be considered as a causal factor for RA-associated ILD, and its [discontinuation] should be discussed through a multidisciplinary discussion," he recommended. In addition, "this study does not investigate the impact of methotrexate use on RA-associated ILD prognosis."

The Danish study did not receive any specific funding, and none of its authors reported having any financial disclosures. The multinational study did not receive any specific funding. Dr. Juge disclosed that he had no relevant conflicts of interest, but many of his coauthors reported financial relationships with industry. Dr. Volkmann disclosed consulting for Boehringer Ingelheim and Forbius, and receiving grant support from Forbius and Corbus.

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SOURCES: Ibfelt EH et al. Ann Rheum Dis. 2020;79(suppl 1):147-8, Abstract OP0232; Juge P-A et al. Ann Rheum Dis. 2020;79(suppl 1):25, Abstract OP0036.

Methotrexate adherence: It's worse than you think

BY BRUCE JANCIN
REPORTING FROM RWCS 2020

MAUI, HAWAII – Results of a carefully conducted real-world study of adherence to oral methotrexate in patients with RA were "kind of scary," Arthur Kavanaugh, MD, said at the 2020 Rheumatology Winter Clinical Symposium.

"At 24 weeks, adherence was only 75%. And these were people who knew they were being monitored, so this is the best of the best. And yet less than 20% took the drug perfectly, meaning they took every dose as it was supposed to be," noted Dr. Kavanaugh, professor of medicine at the University of California, San Diego, and RWCS program director.

Bruce Jancin/MDedge News

Dr. John J. Cush (L) and Dr. Arthur Kavanaugh

"Adherence to methotrexate is really not very good. This is our cornerstone drug – methotrexate – and I think it certainly applies to other medications that we're using," he added.

He and his fellow panelist John J. Cush, MD, discussed the implications of this recent study, led by Kaleb Michaud, PhD, of the University of Nebraska Medical Center, Omaha.

The methotrexate adherence study included 60 patients with RA whose use of the disease-modifying antirheumatic drug (DMARD) over 24 weeks was monitored via the electronic Medication Event Monitoring System. These were motivated patients seen in routine clinical practice: They were participants in Forward, the National Databank for Rheumatic Diseases, and they understood that their use of methotrexate was being monitored.

Among the key findings: Patients on average took their weekly dose as directed for a total of 18 of the 24 weeks, although adherence decreased over time. Overall, 13% of participants missed 1 week, and 68% skipped 2 or more weeks. There was no significant difference in methotrexate adherence between biologic-naive and -experienced patients, nor between those on methotrexate monotherapy versus those on additional medication. Patient demographics and RA severity were similar between patients who missed taking their methotrexate for 2 weeks or more and those who missed fewer or no doses.

Higher Patient Global Assessment of Disease Activity scores were associated with correct dosing. So was being unemployed, having no prior conventional DMARD experience, and having less disability. A higher baseline score on the Beliefs About Medicines Questionnaire Specific-Necessity subscale, which indicates stronger belief in the necessity of the medication, were associated with greater likelihood of appropriate dosing, while lower scores were linked with more weeks of early dosing. However, the other elements of the Beliefs About Medicines Questionnaire weren't significantly associated with adherence (ACR Open Rheumatol. 2019 Sep 6;1[9]:560-70).

"This is a big problem. A lot of factors go into medication nonadherence. The solution has to begin with your relationship with the patient. If you want people to trust you, you're going to have to work at that," observed Dr. Cush, who is professor of medicine and rheumatology at Baylor University Medical Center, Dallas, and director of clinical rheumatology at the Baylor Research Institute.

Roy Fleischmann, MD, a rheumatologist and medical director of the Metroplex Clinical Research Center, Dallas, said that widespread suboptimal adherence to oral methotrexate has important implications for clinical trials. Often the placebo response rate in a randomized trial where the control group is on background methotrexate is so unexpectedly high that the potential efficacy of the active drug is masked; in such situations, it's quite possible that patients who previously weren't taking their methotrexate consistently start doing so when they join a closely supervised study, with a resultant inflated placebo response rate, he said.

One audience member who sees lots of medication-adherence issues in his practice suggested that it might be time to become more aggressive in using intravenous infusion therapy instead of subcutaneously administered agents in patients with active RA and adherence problems.

"Maybe that's why rituximab does so well in the clinical trials," he said.

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

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Low-dose methotrexate trial pins down adverse-event rates seen over nearly 2 years

BY STEVE CIMINO
FROM ANNALS OF INTERNAL MEDICINE

A new study has found an elevated risk of some adverse events in patients treated with low-dose methotrexate, compared with patients treated with placebo.

"The data presented here provide an important source of new evidence to improve the monitoring guidelines and safe prescribing of LD-MTX [low-dose methotrexate]," wrote Daniel H. Solomon, MD, of Brigham and Women's Hospital and Harvard Medical School in Boston, and coauthors. The study was published in Annals of Internal Medicine.

To determine the rates of adverse events (AEs) among LD-MTX users, along with assessing the risks of certain predefined AEs, the researchers enrolled 6,158 patients in the Cardiovascular Inflammation Reduction Trial (CIRT) and randomized 4,786 of those patients to two groups: those receiving LD-MTX (n = 2,391) and those receiving placebo (n = 2,395). The median dose was 15 mg per week, and median follow-up was 23 months. All participants in CIRT had a history of cardiovascular disease, along with diabetes or metabolic syndrome. Just over 81% of the participants were male, and nearly 85% were white. Their median age was nearly 66 years.

Of the participants in the LD-MTX group, 2,156 (90.2%) had an AE and 2,080 (87.0%) had an AE of interest, which included infectious, hematologic, pulmonary, hepatic, cancerous, and gastrointestinal AEs. Of the participants in the placebo group, 2,076 (86.7%) had an AE and 1,951 (81.5%) had an AE of interest. As such, the relative rate of an AE of interest was 17% higher in the LD-MTX group (hazard ratio, 1.17; 95% confidence interval, 1.10-1.25).

In regard to specific types of AEs, the rates of gastrointestinal (HR, 1.23; 95% CI, 1.03-1.47), pulmonary (HR, 1.42; 95% CI, 1.14-1.77), infectious (HR, 1.15; 95% CI, 1.01-1.30), and hematologic (HR, 1.22; 95% CI, 1.11-1.34) were higher for participants in the LD-MTX group. Five cases of cirrhosis were found in the LD-MTX group, compared with none in the placebo group; none of the patients with cirrhosis had severe liver test abnormalities before their diagnosis. While the risk of cancer overall was not elevated in the LD-MTX group, 53 participants in that group developed skin cancer, compared with 26 in the placebo group (HR, 2.04; 95% CI, 1.28-3.26). Renal AEs were among the few that decreased in LD-MTX users (HR, 0.85; 95% CI, 0.78-0.93).


Dr. Solomon

"Methotrexate has become the standard of care for RA patients," Dr. Solomon said in an interview, "and because it worked so well, we accepted it without large placebo-controlled trials and without a precise understanding of the risk factors for AEs. Until this study, our evidence basis for the side-effect profile was relatively weak.

"We had a limited data set but decades of experience," he added. "Now we have better evidence, for example, that methotrexate is associated with elevations in liver function tests. We even found five cases of cirrhosis. And the people who developed cirrhosis didn't have severe test abnormalities; just minor ones over many months. So now we have a better understanding of the potential impact of minor, yet chronic abnormalities."

Dr. Solomon and coauthors acknowledged their study's limitations, including CIRT not including patients with systemic rheumatic disease and the possibility that participants did not report AEs that occurred in between routine study visits. In addition, although the median follow-up of nearly 2 years was longer than in other LD-MTX trials, they noted that "it may still be too short to observe some AEs that require long-term exposure."

Dr. Solomon and colleagues should be commended for undertaking a long-awaited randomized, placebo-controlled trial that adds much-needed insight into how and when to monitor patients being treated with MTX, Vivian P. Bykerk, MD, of the Hospital for Special Surgery and Weill Cornell Medical College in New York, wrote in an editorial (Ann Intern Med. 2020 Feb 17. doi: 10.7326/M20-0435).


Dr. Bykerk

Dr. Bykerk noted that, although the results may not be applicable to patients with RA and other inflammatory arthritides who are treated with MTX – RA patients in particular are younger, more often female, have lower rates of diabetes, and usually receive higher doses than those used in CIRT – the risk estimates from the CIRT study are "largely congruent with those expected in MTX-treated patients with rheumatic diseases."

Regardless, she emphasized that this is a step in a much-needed direction, reminding physicians that "MTX use has inherent risks" and that its AEs, although infrequent, are clinically serious.

The National Institutes of Health funded the study. Various authors reported receiving grants from the National Heart, Lung, and Blood Institute, along with grants, research support, and personal fees from numerous pharmaceutical companies before and during the study. Dr. Bykerk reported receiving personal fees, grants, and nonfinancial support from pharmaceutical companies, foundations, and the NIH.

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SOURCE: Solomon DH et al. Ann Intern Med. 2020 Feb 17. doi: 10.7326/M19-3369.

TNF inhibitors cut odds of VTE in RA patients

BY MAUREEN SALAMON

The risk for venous thromboembolism is almost 50% lower in patients with RA taking tumor necrosis factor (TNF) inhibitors than it was in those taking conventional synthetic disease-modifying antirheumatic drugs (DMARDs), according to data from the German RABBIT registry.


Dr. Strangfeld

"Some rheumatologists have thought TNF inhibitors could increase the risk for venous thromboembolism events, but we don't think this is true, based on our findings," said investigator Anja Strangfeld, MD, PhD, from the German Rheumatism Research Center in Berlin.

The risk is more than one-third lower in RA patients treated with other newer biologics, such as abatacept, rituximab, sarilumab, and tocilizumab.

However, risk for a serious venous thromboembolism is twice as high in patients with C-reactive protein (CRP) levels above 5 mg/L and is nearly three times as high in patients 65 years and older.

For the study, Dr. Strangfeld and her colleagues followed about 11,000 patients for more than 10 years. The findings were presented at the European League Against Rheumatism 2020 Congress.

"Patients with RA have a greater risk for venous thromboembolism compared with the general population, but we didn't know the risk conveyed by different DMARD treatments," Dr. Strangfeld said in an interview. "It is also evident that higher age and lower capacity for physical function increase the risk, which was not so surprising."

Chronic inflammation in RA patients elevates the risk for deep vein and pulmonary thrombosis by two to three times, said John Isaacs, MBBS, PhD, from Newcastle University in Newcastle Upon Tyne, England, who is chair of the EULAR scientific program committee.

Among the supporting studies Dr. Isaacs discussed during an online press conference was a Swedish trial of more than 46,000 RA patients, which had been presented earlier by Viktor Molander, a PhD candidate from the Karolinska Institute in Stockholm (abstract OP0034).

Mr. Molander's team showed that 1 in 100 patients with high disease activity will develop venous thromboembolism within a year, which is twice the number of events seen among patients in remission.

Combined with the RABBIT data, both studies show that, "if you can control their disease in the right way, you're not only helping rheumatoid arthritis patients feel better, but you could be prolonging their lives," Dr. Isaacs said.

> "If you can control their disease in the right way, you're not only helping rheumatoid arthritis patients feel better, but you could be prolonging their lives."

The prospective RABBIT study followed RA patients who began receiving a new DMARD after treatment failed with at least one conventional synthetic DMARD, such as methotrexate or leflunomide. At baseline, those taking TNF inhibitors or other biologics had higher CRP levels on average, as well as a higher rate of existing cardiovascular disease. They also received glucocorticoids, such as prednisone, more often.

The observational nature of the RABBIT study is a weakness, Dr. Strangfeld said, and it could not prove cause and effect. But the methodology had several strengths, including input on patient factors from participating rheumatologists at least every 6 months.

"We enrolled patients at the start of treatment and observed them, regardless of any treatment changes, for up to 10 years," she added. "That's a really long observation period."


Dr. Carmona

The RABBIT data can help shape treatment decisions, said Loreto Carmona, MD, PhD, from the Musculoskeletal Health Institute in Madrid, who is chair of the EULAR abstract selection committee.

For a woman with RA who smokes and takes oral contraceptives, for example, "if she has high levels of inflammation, I think it's okay to use TNF inhibitors, where maybe in the past we wouldn't have thought that," she said.

"The TNF inhibitors are actually reducing the inflammation and, therefore, reducing the risk," Dr. Carmona said in an interview. "It could be an effect of using the drugs on people with higher levels of inflammation. It's an indirect protective effect."

The study was funded by a joint unconditional grant from AbbVie, Amgen, Bristol-Myers Squibb, Fresenius-Kabi, Hexal, Lilly, Merck Sharp & Dohme, Mylan, Pfizer, Roche, Samsung Bioepis, Sanofi-Aventis, and UCB. Dr. Strangfeld is on the speakers bureaus of AbbVie, Bristol-Myers Squibb, Pfizer, Roche and Sanofi-Aventis. Dr. Isaacs is a consultant or has received honoraria or grants from AbbVie, Amgen, Merck, Pfizer, Roche, and UCB. Dr. Carmona has disclosed no relevant financial relationships.

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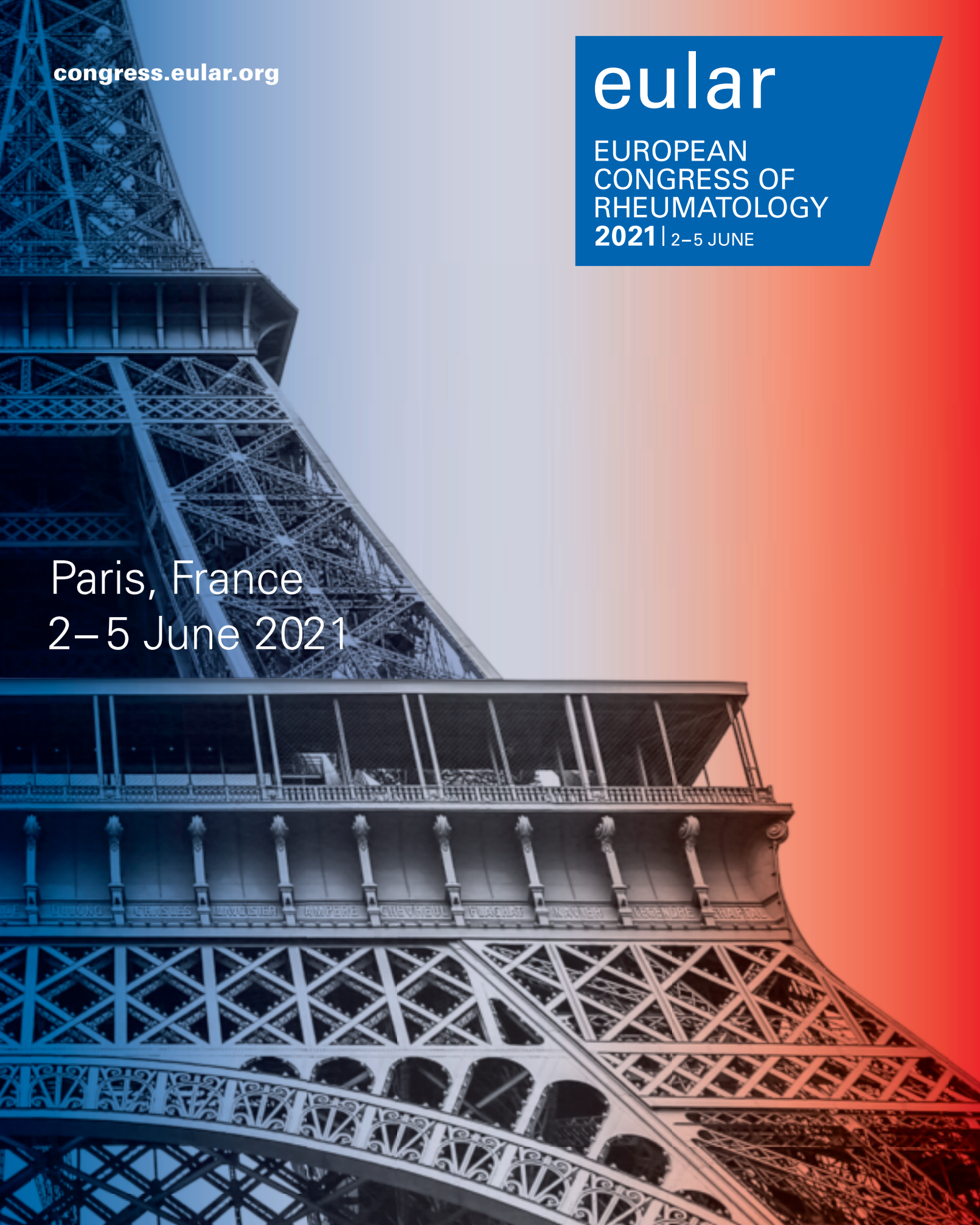

Paris, France
2–5 June 2021

Patients taking tumor necrosis factor inhibitors can safely receive Zostavax

BY JEFF CRAVEN
REPORTING FROM ACR 2019

ATLANTA – A group of patients using a tumor necrosis factor inhibitor safely received the live-attenuated varicella vaccine Zostavax without any cases of herpes zoster in the first 6 weeks after vaccination in the blinded, randomized, placebo-controlled Varicella Zoster Vaccine (VERVE) trial.

According to guidelines from the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, there is a theoretical concern that patients using a tumor necrosis factor inhibitor (TNFi) and other biologic therapies who receive a live-attenuated version of the varicella vaccine (Zostavax) could become infected with varicella from the vaccine. Patients with RA and psoriatic arthritis as well as other autoimmune and inflammatory conditions who are likely to receive TNFi therapy are also at risk for herpes zoster reactivation, Jeffrey Curtis, MD, professor of medicine in the division of clinical immunology and rheumatology of the University of Alabama at Birmingham, said in his presentation at the annual meeting of the American College of Rheumatology. There also exists a risk for patients receiving low-dose glucocorticoids.

"The challenge, of course, is there's not a great definition and there certainly is not a well-standardized assay for how immunocompromised someone is, and so that led to the uncertainty in this patient population for this and other live-virus vaccines," Dr. Curtis said.

No varicella cases in vaccinated patients

Dr. Curtis and colleagues enrolled 627 participants from 33 centers into the VERVE trial. Participants were aged at least 50 years, were taking a TNFi, and had not previously received Zostavax.

Patients in both groups had a mean age of about 63 years and about two-thirds were women. The most common indications for TNFi use in the Zostavax group and the placebo group were RA (59.2% vs. 56.0%, respectively), psoriatic arthritis (24.3% vs. 23.9%), and ankylosing spondylitis (7.2% vs. 8.5%), while the anti-TNF agents used were adalimumab (38.1% vs. 27.4%), infliximab (28.4% vs. 34.2%), etanercept (19.0% vs. 23.5%), golimumab (10.0% vs. 8.1%), and certolizumab pegol (4.5% vs. 6.8%).


Dr. Curtis

In addition, some patients in the Zostavax and placebo groups were also taking concomitant therapies with TNFi, such as oral glucocorticoids (9.7% vs. 11.4%).

The researchers randomized participants to receive Zostavax or placebo (saline) and then followed them for 6 weeks, and looked for signs of wild-type or vaccine-strain varicella infection. If participants were suspected to have varicella, they were assessed clinically, they underwent polymerase chain reaction testing, and rashes were photographed. At baseline and at 6 weeks, the researchers collected serum and peripheral blood mononuclear cells to determine patient immunity to varicella. After 6 months, participants were unmasked to the treatment arm of the study.

Dr. Curtis and colleagues found no confirmed varicella infection cases at 6 weeks. "To the extent that 0 cases out of 317 vaccinated people is reassuring, there were no cases, so that was exceedingly heartening as a result," he said.

Out of 20 serious adverse events total in the groups, 15 events occurred before 6 months, including 8 suspected varicella cases in the Zostavax group and 7 in the placebo group. However, there were no positive cases of varicella – either wild type or vaccine type – after polymerase chain reaction tests. Overall, there were 268 adverse events in 195 participants, with 73 events (27.2%) consisting of injection-site reactions. The researchers also found no difference in the rate of disease flares, and found no differences in adverse reactions between groups, apart from a higher rate of injection-site reactions in the varicella group (19.4% vs. 4.2%).

With regard to immunogenicity, the humoral immune response was measured through IgG, which showed an immune response in the varicella group at 6 weeks (geometric mean fold ratio, 1.33; 95% confidence interval, 1.18-1.51), compared with the placebo group (GMFR, 1.02; 95% CI, 0.91-1.14); cell-mediated immune response was measured by interferon-gamma, which also showed an immune response in the live-vaccine group (GMFR, 1.49; 95% CI, 1.14-1.94), compared with participants who received placebo (GMFR, 1.14; 95% CI, 0.87-1.48). In preliminary 1-year data, IgG immune response was elevated in the varicella group (GMFR, 1.46; 95% CI, 1.08-1.99), but there was no elevated immune response for interferon-gamma (GMFR, 0.78; 95% CI, 0.49-1.25).

"I think the trial is encouraging not only for its result with the live zoster vaccine and TNF-treated patients, but also challenge the notion that, if you need to, a live-virus vaccine may in fact be able to be safely given to people with autoimmune and inflammatory diseases, even those treated with biologics like tumor necrosis factor inhibitors," he said.

Dr. Curtis noted that a new trial involving the recombinant, adjuvanted zoster vaccine (Shingrix) is currently in development and should begin next year.

The VERVE trial was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Dr. Curtis reported serving as a current member of the Center for Disease Control and Prevention's Advisory Committee on Immunization Practices Herpes Zoster Work Group. He and some of the other authors reported financial relationships with many pharmaceutical companies.

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SOURCE: Curtis J et al. Arthritis Rheumatol. 2019;71(suppl 10), Abstract 824.

TNF inhibitors may up inflammatory CNS event risk

BY DEBORAH BRAUSER

Use of tumor necrosis factor (TNF) inhibitors in patients with autoimmune diseases may increase risk for inflammatory central nervous system outcomes, new research suggests.

The nested case-control study included more than 200 participants with diseases such as rheumatoid arthritis, psoriasis, and Crohn's disease. Results showed that exposure to TNF inhibitors was significantly associated with increased risk for demyelinating CNS events, such as multiple sclerosis, and nondemyelinating events, such as meningitis and encephalitis.

Interestingly, disease-specific secondary analyses showed that the strongest association for inflammatory events was in patients with rheumatoid arthritis.

Lead author Amy Kunchok, MD, of Mayo Clinic, Rochester, Minn., noted that "these are highly effective therapies for patients" and that these CNS events are likely uncommon.

"Our study has observed an association, but this does not imply causality. Therefore, we are not cautioning against using these therapies in appropriate patients," Dr. Kunchok said in an interview.

"Rather, we recommend that clinicians assessing patients with both inflammatory demyelinating and nondemyelinating CNS events consider a detailed evaluation of the medication history, particularly in patients with coexistent autoimmune diseases who may have a current or past history of biological therapies," she said.

The findings were published in JAMA Neurology (2020;77[8]:937-946).

Not well understood

TNF inhibitors "are common therapies for certain autoimmune diseases," the investigators noted.

Previously, a link between exposure to these inhibitors and inflammatory CNS events "has been postulated but is poorly understood," they wrote.

In the current study, they examined records for 106 patients who were treated at Mayo clinics in Minnesota, Arizona, or Florida from January 2003 through February 2019. All participants had been diagnosed with an autoimmune disease that the Food and Drug Administration has listed as an indication for TNF-inhibitor use. This included rheumatoid arthritis (n = 48), ankylosing spondylitis (n = 4), psoriasis and psoriatic arthritis (n = 21), Crohn's disease (n = 27), and ulcerative colitis (n = 6). Their records also showed diagnostic codes for the inflammatory demyelinating CNS events of relapsing-remitting or primary progressive multiple sclerosis, clinically isolated syndrome, radiologically isolated syndrome, neuromyelitis optica spectrum disorder, and transverse myelitis; or for the inflammatory nondemyelinating CNS events of meningitis, meningoencephalitis, encephalitis, neurosarcoidosis, and CNS vasculitis. The investigators also included 106 age-, sex-, and autoimmune disease–matched participants 1:1 to act as the control group.

In the total study population, 64% were women and the median age at disease onset was 52 years. In addition, 60% of the patient group and 40% of the control group were exposed to TNF inhibitors.

Possible novel finding

Results showed that TNF-inhibitor exposure was significantly linked to increased risk for developing any inflammatory CNS event (adjusted odds ratio, 3.01; 95% CI, 1.55-5.82; $P = .001$). When the outcomes were stratified by class of inflammatory event, these results were similar. The aOR was 3.09 (95% CI, 1.19-8.04; $P = .02$) for inflammatory demyelinating CNS events and was 2.97 (95% CI, 1.15-7.65; $P = .02$) for inflammatory nondemyelinating events.

Dr. Kunchok noted that the association between the inhibitors and nondemyelinating events was "a novel finding from this study."

In secondary analyses, patients with rheumatoid arthritis and exposure to TNF inhibitors had the strongest association with any inflammatory CNS event (aOR, 4.82; 95% CI, 1.62-14.36; $P = .005$).

A pooled cohort comprising only the participants with the other autoimmune diseases did not show a significant association between exposure to TNF inhibitors and development of CNS events ($P = .09$).

"Because of the lack of power, further stratification by individual autoimmune diseases was not analyzed," the investigators reported.

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Although the overall findings showed that exposure to TNF inhibitors was linked to increased risk for inflammatory events, whether this association "represents de novo or exacerbated inflammatory pathways requires further research," the authors wrote.

Dr. Kunchok added that more research, especially population-based studies, is also needed to examine the incidence of these inflammatory CNS events in patients exposed to TNF inhibitors.

Adds to the literature

In an accompanying editorial (JAMA Neurol. 2020;77[8]:933-5), Jeffrey M. Gelfand, MD, department of neurology at the University of California, San Francisco, and Jinoos Yazdany, MD, MPH, division of rheumatology at the University of California, San Francisco, noted that, although the study adds to the literature, the magnitude of the risk

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Biologic DMARDs appear as effective in elderly-onset RA as in young-onset RA

BY SHARON WORCESTER
REPORTING FROM ACR 2019

ATLANTA – Elderly-onset and young-onset rheumatoid arthritis patients initiating treatment with biologic disease-modifying antirheumatic drugs (bDMARDs) respond similarly with respect to clinical improvement at 48 weeks and adverse events, data from a large registry in Japan suggest.

The findings have important implications – particularly for elderly-onset rheumatoid arthritis patients, who tend to present with higher disease activity levels and increased disability, but who nevertheless receive biologics less frequently, compared with young-onset RA patients, according to Sadao Jinno, MD, of the department of rheumatology and clinical immunology, Kobe University Graduate School of Medicine, Osaka, Japan, and colleagues.

The findings were presented in a poster at the annual meeting of the American College of Rheumatology.

Of 7,183 participants in the multicenter observational registry, 989 who initiated bDMARDs and who had a DAS28-erythrocyte sedimentation rate score of at least 3.2 at the time of initiation were included in the current analysis. The proportion of elderly-onset RA patients in the registry was 36.8%, and the proportion of elderly-onset RA patients using bDMARDs was significantly lower than that among young-onset RA patients (18.3% vs. 28.0%; *P* less than .001), Dr. Jinno and colleagues reported.


Sharon Worcester/MDedge News
Dr. Sadao Jinno

However, after adjustment for differences in baseline characteristics between the two age groups, no significant difference was seen in Clinical Disease Activity Index (CDAI) score at 48 weeks (odds ratio, 1.01), Dr. Jinno said during a press conference highlighting the findings.

A trend toward lower remission rates was observed in the early-onset patients (OR, 0.52; $P = 1.10$). The low–disease activity/remission rate was similar in the groups after adjustment for multiple confounders (OR, 0.86; $P = 0.77$), he said, adding that drug-maintenance rates and adverse event–related discontinuation rates also were similar in the groups (hazard ratio, 0.95; $P = 0.78$ for drug maintenance; HR, 0.78; $P = 0.22$ for discontinuation).

Patients were enrolled in the multicenter observational registry between September 2009 and December 2017, and those with onset at age 60 years or older were considered to have elderly-onset RA.

"In my daily practice, I see a lot of patients with elderly-onset RA who are treated with biologics very effectively and safely," he said. "So we wanted to see if there really is any difference [in outcomes] between the elderly-onset patients and the young-onset patients."

The findings suggest they can be treated as effectively and safely as younger patients, he said.

In a press release, he further stated that clinicians should "choose wisely which patients with elderly-onset RA are safely treated with biologics given that they are still at risk of developing adverse events, especially infections."

Conversely, it is important to keep in mind that dysfunction in elderly-onset RA patients may worsen without timely biologic treatment, he noted.

Dr. Jinno and colleagues reported having no relevant disclosures.

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SOURCE: Jinno S et al. Arthritis Rheumatol. 2019;71(suppl 10), Abstract 1345.

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found "remains unclear."

Dr. Gelfand and Dr. Yazdany said they agree with Dr. Kunchok that "next steps should include population-based observational studies that control for disease severity."

Still, the study provides additional evidence of rare adverse events in patients receiving TNF inhibitors, they noted. So how should prescribers proceed?

"As with all treatments, the risk-benefit ratio for the individual patient's situation must be weighed and appropriate counseling must be given to facilitate shared decision-making discussions," wrote the editorialists.

In addition, neurologic consultation can be helpful for clarifying diagnoses and providing advice on monitoring strategies for TNF-inhibitor treatment in those with possible MS or other demyelinating conditions, they noted.

The study was funded by a grant from the National Center for Advancing Translational Sciences. Dr. Kunchok reports having received research funding from Biogen outside this study. A full list of disclosures for the other study authors is in the original article. Dr. Gelfand reports having received grants for a clinical trial from Genentech and consulting fees from Biogen, Alexion, Theranica, Impel Neuropharma, Advanced Clinical, Biohaven, and Satsuma. Dr. Yazdany reports having received grants from Pfizer and consulting fees from AstraZeneca and Eli Lilly outside the submitted work.

A version of this article originally appeared on Medscape.com.

Studies forge stronger links between rheumatoid arthritis and asthma, COPD

BY ANDREW D. BOWSER
FROM ARTHRITIS & RHEUMATOLOGY

Asthma and chronic obstructive pulmonary disease were both linked to an increased risk of rheumatoid arthritis in a recent large, prospective cohort study, researchers have reported, which adds to a growing body of evidence that airway inflammation is implicated in the development of this disease.

RA risk was increased by about 50% among asthma patients, even when excluding those who had ever smoked, according to the study's results, which were based on more than 200,000 women in the Nurses' Health Study I and II.

Risk of RA nearly doubled among those with chronic obstructive pulmonary disease (COPD), with an even stronger association seen in older ever-smokers, according to authors of the study.

The findings not only strengthen the case for the potential role of obstructive lung diseases in RA development, according to the study's authors, but also suggest that health care providers need to lower the bar for evaluation of patients with lung diseases and inflammatory joint symptoms.

"If these patients develop arthralgias, then the clinicians taking care of them should have a low threshold to consider RA, and perhaps refer, or check these patients with a diagnostic test for RA," said researcher Jeffrey A. Sparks, MD, of Brigham and Women's Hospital and Harvard Medical School in Boston.

What's perhaps not as clear now is whether screening obstructive lung disease patients in the absence of early RA signs would be warranted: "I don't know if we're quite at the point where we would need to screen these patients if they're not symptomatic," Dr. Sparks said in an interview.

The study by Dr. Sparks and colleagues is, by far, not the first study to implicate asthma or other lung conditions in RA development. However, most previous studies are retrospective, and interpretation of the findings has been subject to limitations such as inadequate power to detect an increased risk or lack of adjustment for important confounding factors, such as smoking.

As such, the study by Dr. Sparks and colleagues is believed to be the first-ever prospective study to evaluate asthma and COPD as risk factors for RA, study authors reported in Arthritis & Rheumatology.


Dr. Sparks

Researchers were able to identify 1,060 incident RA cases that developed in 15,148 women with asthma and 3,573 with COPD in the study with more than 4 million person-years of follow-up.

The association between asthma and increased RA risk was seen not only for the asthma population as a whole (hazard ratio, 1.53; 95% confidence interval, 1.24-1.88), but also for the subset of women who had never smoked, to a similar degree (HR, 1.53; 95% CI, 1.14-2.05), the report shows.

COPD's association with RA risk was apparent overall (HR, 1.89; 95% CI, 1.31-2.75) and even more so in the subgroup of ever-smokers 55 years of age and older (HR, 2.20; 95% CI, 1.38-3.51), the data further show.

Findings of studies looking at the inflammation of airways and other mucosal sites are "critically important to understand" when it comes to trying to prevent RA, said Kevin Deane, MD, of the University of Colorado at Denver at Aurora.

"If we indeed are trying to prevent rheumatoid arthritis in terms of the joint disease, we may need to look at these mucosal sites in individuals who don't yet have joint disease as potential sites to target for prevention, or at least areas to study to understand how prevention may work," said Dr. Deane, principal investigator on the National Institutes of Health–funded Strategy for the Prevention of RA (StopRA) trial.

With that in mind, it's conceivable targeting a lung process might prevent joint disease in a patient with asthma or airway inflammation and blood markers that indicate a risk of RA, Dr. Deane said in an interview.


Dr. Deane

Blood markers of RA have been evaluated in some recent studies, with findings that provide further evidence of a link between lung diseases and RA, and vice versa.

In particular, anti–citrullinated protein antibodies (ACPA) are clearly central to RA pathogenesis. And while asthma is increasingly linked to RA risk, there have been relatively few data on any potential links between ACPA and asthma.

That research gap led to a case-control study of the Nurses' Health Study I and II (on which Dr. Sparks was senior author) showing that asthma was strongly linked to elevated ACPA in blood drawn from patients prior to a diagnosis of RA.

Results, published last year in Arthritis Research & Therapy, showed a significant association between asthma and pre-RA ACPA elevation (odds ratio, 3.57; 95% CI, 1.58-8.04), after adjustment for smoking and other potentially confounding factors. Investigators said the findings provided evidence that chronic mucosal airway inflammation is a factor in the development of ACPA and in the pathogenesis of RA.

In a follow-up study published more recently in Arthritis Care & Research,

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Price increases for RA biologics keep out-of-pocket costs high for Medicare patients

BY STEVE CIMINO
FROM JAMA NETWORK OPEN

Although the 2010 Patient Protection and Affordable Care Act attempted to close the coverage gap for prescription drugs, a new study has found that yearly price increases for expensive treatments like rheumatoid arthritis biologics have kept out-of-pocket spending high for patients enrolled in Medicare Part D.

"As the coverage gap is now considered closed, our results suggest a need for out-of-pocket maximums in the catastrophic phase to limit older Americans' yearly financial burden and allow them to better estimate their annual drug costs," wrote coauthors Alexandra Erath and Stacie B. Dusetzina, PhD, of Vanderbilt University in Nashville, Tenn. The study was published in JAMA Network Open.

To determine if closing the Medicare Part D coverage gap lowered out-of-pocket costs as anticipated, the researchers embarked on a cross-sectional study of Medicare data from the first quarter of each calendar year from 2010 to 2019. They analyzed the costs of 17 RA biologic drug and strength combinations, calculating the median point-of-sale price per fill for each drug and adjusting for medical inflation.

From 2010 to 2019, the median price per fill increased for all 17 drugs studied. With the exception of the 100-mg/1-mL golimumab (Simponi) autoinjector, every drug that had been on the market for 5 years or longer had a price increase of more than 20%. For the six drugs that have been on the market since 2010 – 200 mg of certolizumab pegol (Cimzia), 25 mg of etanercept (Enbrel), 50 mg of etanercept, 20 mg/0.4 mL of adalimumab (Humira), 40 mg/0.8 mL of adalimumab, and 50 mg/0.5 mL of golimumab – the median list price increased by a mean of 160% (standard deviation, 17%; range, 136%-180%).

> In 2010-2019, all but one of the drugs that had been on the market for at least 5 years had a price increase of > 20%.

Mean (SD) annual out-of-pocket spending for those six drugs did decrease from $6,108 (SD, $234; range, $5,647-6,282) in 2010 to $4,801 (SD, $620; range, $3,594-$5,196) in 2019. However, the most significant decrease actually occurred between 2010 and 2011, when out-of-pocket spending dropped to $4,026 because the Affordable Care Act's 50% manufacturer rebate for brand-name drugs filled in the coverage gap. This meant there was actually a mean increase of 19% in out-of-pocket costs from 2011 to 2019.

"This is the same story as the EpiPen," said Maria Greenwald, MD, of Desert Medical Advances in Palm Desert, Calif., in an interview. "Patients have to have it, so you're going to pay $600 even if you used to pay $50. Why do pharmaceutical companies keep raising their prices? Because they can. There's no cap on list prices. And these drugs are miracles. They're the difference between a high quality of life and being bound to a wheelchair. These patients don't sleep without them. They'll do whatever they can to pay for them, and so the prices continue to go up."

The authors shared their study's potential limitations, including relying on list prices that do not factor in rebates and focusing on a single biologic filled every month rather than all treatments filled under Medicare, which could "result in our underestimating out-of-pocket spending by patients."

The study was supported by the Commonwealth Fund and the Leukemia and Lymphoma Society. Dr. Dusetzina reported receiving grants from Arnold Ventures and personal fees from the Institute for Clinical and Economic Review.

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SOURCE: Erath A et al. JAMA Netw Open. 2020 Apr 27. doi: 10.1001/jamanetworkopen.2020.3969.

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investigators showed that, among women in the Nurses Health Study I and II, pre-RA ACPA elevation was linked to increased risk of COPD, compared with controls (HR, 3.04; 95% CI, 1.33-7.00), while the risk for development of asthma was similar in women with or without elevated pre-RA ACPA.

That study was in part an attempt to establish a "timeline" related to antibodies, lung diseases, and RA onset, Dr. Sparks said in the interview.

"We think that probably the asthma is more important in developing the antibody, but that once you have the antibody, if you didn't have asthma by then, you're unlikely to develop it," he said. "So asthma seems to be something that could happen before the antibody production, whereas COPD seems to happen after – but ACPA seems to be the common link in both of these obstructive lung diseases."

The study in Arthritis & Rheumatology linking asthma and COPD to risk of incident RA was supported by the National Institutes of Health. Dr. Sparks reported grant support from Amgen and Bristol Myers Squibb and consulting fees from Inova and Optum. Coauthors provided disclosures related to GlaxoSmithKline, AstraZeneca, Merck, Neutrolis, and Genentech.

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Differentiating hypersensitivity reactions to monoclonal antibodies

BY BRUCE JANCIN
REPORTING FROM RWCS 2020

MAUI, HAWAII – Desensitization is a powerful and effective tool in patients with certain types of hypersensitivity reactions to therapeutic monoclonal antibodies, but it's best considered a last resort reserved for individuals with no options left other than the offending biologic, Anna Postolova, MD, said at the 2020 Rheumatology Winter Clinical Symposium.

Why so selective? Desensitization is considered a high-risk intervention. It's typically done as an inpatient procedure involving an overnight hospital stay followed by an elaborate 12-step protocol involving administration of small quantities of the culprit biologic in ascending concentrations over a 5- to 6-hour period.

Moreover, for an intravenous agent, such as infliximab (Remicade), desensitization has to be repeated prior to giving every dose of the biologic. So it makes sense to skip desensitization and simply switch to an alternative tumor necrosis factor inhibitor or a different class of biologic unless experience has shown that the culprit monoclonal antibody is the only one that works for that patient. It's known, for example, that infliximab has no crossreactivity with adalimumab (Humira), explained Dr. Postolova, a dual rheumatologist and allergist/immunologist at Stanford (Calif.) University.

Definition of type and severity of the hypersensitivity reaction

Dr. Postolova favors the hypersensitivity reaction classification system developed by Mariana Castells, MD, PhD, and coworkers at Brigham and Women's Hospital, Boston (J Allergy Clin Immunol. 2018 Jul;142[1]:159-70.e2.).

They divide the field into immediate and delayed hypersensitivity reactions. Immediate hypersensitivity reactions arise rapidly, between minutes and a few hours. They can be categorized as infusion reactions, cytokine-release reactions, and IgE-mediated reactions. Phenotypically, infusion reactions and cytokine-release reactions are typically characterized by various combinations of chills, fever, flushing, hypertension, tachycardia, nausea, vomiting, syncope, and shortness of breath.

Bruce Jancin/MDedge News

Dr. Anna Postolova

IgE-mediated reactions can also involve flushing and shortness of breath, and in addition itch, urticaria, and hypotension. These are anaphylactic reactions. Neither hypertension nor fever is part of the anaphylactic picture; those findings point instead to an infusion reaction or cytokine-release reaction.

Most allergists grade reaction severity on a 1-3 scale. Grade 1 reactions are considered mild and involve symptoms limited to the skin, such as flushing, or a single other organ system.

"That being said, if my patient is having a reaction with bronchospasm, I consider that a moderate, grade 2 reaction, and I stop the infusion. There's only so much you can do for bronchospasm. It's a very serious reaction," Dr. Postolova observed.

Grade 2 reactions ordinarily involve two or more organ systems, but without hypotension or cyanosis. Grade 3 reactions are severe anaphylactic reactions with cardiovascular and/or neurologic compromise.

Delayed hypersensitivity reactions are of two types: serum sickness–like reactions and type IV cell-mediated mucocutaneous reactions.

Type IV reactions can range from a mild maculopapular rash to erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS (drug reaction with eosinophilia and systemic symptoms). Onset of type IV reactions can occur after 12 hours up to several weeks after exposure.

Serum sickness–like reactions typically begin 5-7 days after the infusion. These reactions are marked by evidence of immune overactivation: fever, arthralgia, arthritis, malaise, purpura, skin rash, and even renal failure.

Management of reactions

A patient with a grade 3 reaction who needs to continue using the culprit monoclonal antibody should be referred to an allergist for skin testing in an effort to identify an IgE-mediated reaction.

The timing of the referral for skin testing is important: The allergist wants to test roughly 4-6 weeks after the hypersensitivity reaction. Test too early and the results will be uninformative because the patient will still be anergic. On the other hand, after 7-8 weeks the patient will have lost the allergy. So there is a sweet spot.

If the patient is skin test positive – with the caveat that skin testing in this setting is not well validated – then the allergist will suggest desensitization, usually as an inpatient.

In contrast, infusion reactions can be handled in the rheumatologist's infusion center. They are self-limited upon repeat exposure with premedication using antihistamines, NSAIDs, oral or injectable steroids, and perhaps montelukast (Singulair).

If a patient initially thought to have an infusion reaction continues to expe-

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Seropositivity in RA linked with doubled pneumonia incidence

BY MITCHEL L. ZOLER, PHD
FROM THE EULAR 2020 E-CONGRESS

Seropositive RA patients had twice the risk for developing pneumonia, compared with seronegative patients, in a study of more than 4,000 RA patients from a single U.S. medical system.

"Patients with seropositive RA, particularly RF [rheumatoid factor]-positive RA, had increased risk for pneumonia throughout the RA disease course that was not explained by measured confounders, including smoking status, multimorbidity, medications, and [erythrocyte sedimentation rate] level," Jeffrey A. Sparks, MD, a rheumatologist at Brigham and Women's Hospital Harvard Medical School in Boston, said at the annual European Congress of Rheumatology.

Dr. Sparks' study used a database of more than 60,000 patients diagnosed with RA as of November 2013 in the records of a large Boston-area medical system that includes physicians affiliated with Brigham and Women's Hospital and Massachusetts General Hospital. The researchers applied a validated algorithm for calculating a patient's probability of having RA, and at the level of 97% probability they narrowed the cohort down to just under 10,000 patients. Additional winnowing because of missing data or a history of pneumonia yielded a study group of 4,110, which included 3,279 (80%) who were seropositive for either or both CCP and RF, and 831 (20%) who were seronegative.

> CCP seropositivity had no statistically significant link with incident pneumonia, while RF seropositivity linked with a roughly twofold higher rate.

During a median follow-up of 7.8 years and total follow-up of more than 32,000 patient-years, the overall pneumonia incidence was 5.8%, with a 2.8% rate among the seronegatives and a 6.6% rate among seropositives. After adjustment for age, sex, glucocorticoid use, disease-modifying antirheumatic drug use, and several other possible confounders, the researchers calculated a 99% relative increased rate of pneumonia among all seropositive patients, compared with the seronegatives ones.

Further analysis looked at pneumonia incidence rates among patients positive only for CCP antibody, positive only for RF antibody, or both, compared with seronegative patients. This showed that CCP seropositivity had no statistically significant link with incident pneumonia, while RF seropositivity linked with a statistically significant, roughly twofold higher rate. Only 6% of all seropositive patients were positive only for CCP antibody, 59% were positive specifically for RF antibody, and 35% for both.

The study had no commercial funding. Dr. Sparks had no disclosures.

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SOURCE: Sparks JA et al. Ann Rheum Dis. 2020 Jun;79(suppl 1):73, Abstract OP0111.

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rience reactions even after the biologic is being delivered more slowly and under the protection of premedication, it's time to consider the possibility that what's really going on is a cytokine-release reaction or an IgE-mediated reaction. Diagnostic skin testing is in order.

For a skin test–negative patient with a suspected cytokine-release reaction, the allergist may propose a therapeutic challenge. This is reserved for patients who the allergist believes will not experience an immediate reaction, and unlike desensitization it's not an intervention intended to induce drug tolerance. The challenge involves giving 10% of a full dose of the biologic, waiting in the allergist's office for 30-60 minutes, then giving the other 90% of the medication, followed by an hour of in-office observation.

The solution to severe type IV delayed hypersensitivity reactions is strict medication avoidance, not desensitization, according to Dr. Postolova.

Top offending monoclonal antibodies

Infliximab and rituximab (Rituxan) are the most common culprits when it comes to immediate hypersensitivity reactions. About 10% of infliximab-treated patients develop these reactions. Although the reaction can occur with the first dose, the peak incidence is with the seventh infusion. Patients with anti-infliximab IgG antibodies are at 140%-300% increased risk; however, concomitant disease-modifying antirheumatic drug therapy lessens that risk.

Infusion reactions or cytokine-release reactions occur upon the first infusion of rituximab in about 25% of treated rheumatology patients and in a higher proportion of cancer patients. Most of these reactions are mild and don't recur when the biologic is administered more slowly and with premedication. Severe recurrent reactions upon subsequent exposure are much more likely to be an IgE-mediated hypersensitivity reaction.

"Stop the medication, send the patient to your local allergist for skin testing, and they'll use a desensitization protocol if rituximab is the best drug for your patient," Dr. Postolova advised.

She reported having no financial conflicts regarding her presentation.

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Repeat LTBI testing most cost effective in patients on biologics who have new risk factors

BY JEFF CRAVEN
REPORTING FROM ACR 2019

ATLANTA – Patients taking biologics who received latent tuberculosis testing on an annual basis were unlikely to convert from a negative QuantiFERON test to a positive result, which suggests that the test may be unnecessary for patients without new tuberculosis risk factors, according to research presented at the annual meeting of the American College of Rheumatology.

In addition, nearly all of the cost of repeat testing for latent tuberculosis infection (LTBI) went to patients who were not diagnosed with or treated for LTBI, noted Urmi Khanna, MD, a dermatologist with the Cleveland Clinic.

"All in all, about $1.4 million U.S. dollars was spent just on additional QuantiFERON testing, and only 1% of this additional cost was actually spent on testing patients who were diagnosed with and treated for latent tuberculosis," Dr. Khanna said in her presentation at the meeting.

"Based on this study, we would like to propose that, in low-incidence TB regions such as the United States, repeat LTBI testing in patients on biologic therapies should be focused on patients who have new risk factors for TB infection since their last screening," she said.

The National Psoriasis Foundation has recommended patients be screened annually for LTBI, and the Centers for Disease Control and Prevention and the ACR have recommended patients taking biologics be screened annually for LTBI if they have new risk factors for TB, such as coming into contact with immigrants, a person infected with TB, immunosuppressed individuals, or persons working in areas where TB might be present. Annual screening was also recently added to the Medicare Merit-Based Incentive Payment System (MIPS), which will affect physician reimbursement. "Based on [the addition of this quality outcome measure], we expect that more and more physicians will adopt this practice of annual LTBI screening in all patients on biologics," Dr. Khanna said.

She and her colleagues examined QuantiFERON tuberculosis test (QFT) results of 10,914 patients from the Cleveland Clinic Foundation between August 2007 and March 2019 where patients were receiving systemic biologic therapy for inflammatory or autoimmune conditions, including nearly 32% with inflammatory bowel disease, 29% with rheumatoid arthritis, and 25% with psoriatic disease. Overall, 5,212 patients were included in the final analysis, and patients had a median of three QFT results. Patients had a median age of 41 years, had taken an average of 1.80 biologics during follow-up, and had a median biologic therapy duration of about 49 months. The most common biologics used were adalimumab (33%), etanercept (17%), and infliximab (17%).

> In a single-center study, nearly all the cost of repeat testing during 2007-2019 went to patients who were not diagnosed or treated for LTBI.

Of these patients, 4,561 patients had negative QFTs (88%), 172 patients had one or more positive QFTs (3%), and 479 patients had one or more indeterminate QFTs (9%). For patients who converted from a negative QFT to a positive QFT, the most common risk factors were exposure to someone with TB (26%), immigration or travel to an endemic area (26%), and occupational exposure (16%).

Within the group with one or more positive QFTs, there were 108 patients with baseline positive QFTs prior to starting biologic therapy (2.1%), 61 patients who converted from a baseline negative QFT to a positive QFT (1.2%), and 3 patients where a positive result overlapped with a negative result (0.1%). The majority of patients who converted to a positive QFT result had borderline positive results (70.5%), defined as 0.35-1 IU/mL, compared with 29.5% of converters who had a positive QFT result of more than 1.0 IU/mL.

Among the 61 patients who converted to a positive QFT result, 28 patients with LTBI (46%) and 1 patient with an active case of TB (2%) were diagnosed and treated. The active TB case was a 29-year-old patient with inflammatory bowel disease and ankylosing spondylitis receiving adalimumab who had recently traveled to India.

The researchers also examined the cost of additional QFTs in each group. Among negative QFTs, the cost of an additional 9,611 tests was $1,201,375. The cost of additional tests for indeterminate QFTs was $136,200, but Dr. Khanna noted that 99.99% of additional tests in this group were for patients never diagnosed with or treated for LTBI. Additional tests for positive QFTs cost another $47,700, and 26.1% of patients in this group were diagnosed and received treatment for LTBI, compared with 73.9% who did not receive an LTBI diagnosis or treatment.

In the discussion session following the presentation, Dr. Khanna emphasized that discontinuing annual screening in low-risk patients was not standard of care at the Cleveland Clinic, and this study was conducted to raise awareness of focusing testing on patients with new TB risk factors.

Dr. Khanna reported no relevant financial disclosures. A few of her coauthors reported financial relationships with pharmaceutical companies.

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SOURCE: Khanna U et al. Arthritis Rheumatol. 2019;71(suppl 10), Abstract 1802.

Steroids linked to increased risk of hypertension

BY DIANA SWIFT

Although the adverse effects of systemic glucocorticoids (GCs) are well known, their association with hypertension in rheumatoid arthritis has been unclear. Now, a large population-based study shows that the drugs are linked to a 17% overall increased risk for incident hypertension among patients with RA.

Further, when the researchers stratified participants by dose category, they found that doses higher than 7.5 mg were significantly associated with hypertension. Cumulative dosage was not tied to any clear pattern of risk.

The authors, led by Ruth E. Costello, a researcher at the Centre for Epidemiology Versus Arthritis in the Centre for Musculoskeletal Research at the University of Manchester (England) concluded that patients who are taking these drugs for the treatment of RA should be monitored for high blood pressure, which is an important but modifiable cardiovascular risk factor, and treated appropriately.

The results of Ms. Costello and colleagues' study were published June 27 in Rheumatology (doi: 10.1093/rheumatology/keaa209).

"While fractures associated with these steroid drugs are well studied, hypertension is a side effect that seems to have been less well studied, and yet it is an important cardiovascular risk factor that can be managed," Ms. Costello said in an interview.

To better understand the possible association, Ms. Costello and colleagues identified 17,760 patients who were newly diagnosed with RA between 1992 and 2019 and were included in the Clinical Practice Research Datalink, which represents about 7% of the U.K. population. None of the patients had hypertension at initial RA diagnosis. Slightly more than two-thirds were women (68.1%), and the mean age was 56.3 years.

Of those patients, 7,421 (41.8%) were prescribed GCs during postdiagnosis follow-up. Most patients (73%) were followed for at least 2 years.

Patients who used GCs were slightly older than never-users (mean age, 57.7 vs. 55.3 years), were predominantly women, had a history of smoking, and had more comorbidities.

The overall incidence rate (IR) of hypertension was 64.1 per 1,000 person-years (95% confidence interval, 62.5-65.7). There were 6,243 cases of incident hypertension over 97,547 person-years of follow-up.

Among those exposed to GCs, 1,321 patients developed hypertension, for an IR of 87.6 per 1,000 person-years.

> "Our results suggest we should be vigilant in patients on all doses of GC, especially higher doses."

Among unexposed participants, the IR for hypertension was 59.7 per 1,000 person-years. In Cox proportional hazards modeling, GC use was associated with a 17% increased risk for hypertension (hazard ratio, 1.17; 95% CI, 1.10-1.24).

The researchers noted that 40% of GC users with hypertension were not prescribed an antihypertensive agent at any point during the study. "Whilst some may have been offered lifestyle advice, left untreated this has important implications in terms of addressing modifiable risk factors in an RA population already at increased risk of CV disease," they wrote.

They noted that cardiovascular disease is a major driver of the elevated mortality risk seen among adults with RA compared with the general population and that recent treatment recommendations address management of cardiovascular risks in these patients (Ann Rheum Dis. 2017;76[1]:17-28).

"There are several routes by which GCs may promote cardiovascular disease, including hypertension, metabolic changes, diabetes, and weight gain. We don't currently know the extent to which each of these individual mechanisms may be increasing cardiovascular disease," said Ms. Costello.

"Glucocorticoids increase fluid retention and promote obesity and hypertension," said Rajat S. Bhatt, MD, a rheumatologist at Prime Rheumatology and Memorial Hermann Katy Hospital in Richmond, Tex., who sees hypertension in GC users in his clinical practice. "So patients need to be monitored for these risk factors," he said in an interview.

Although hypertension may be a significant factor in the increase in cardiovascular disease in the RA population, Dr. Bhatt said the major driver is likely the intrinsic inflammatory state caused by the disease itself. As to why the GC-hypertension connection has flown under the radar in RA, he added, "That specific link has been difficult to tease out since RA patients are often on multiple medications."

In regard to the role of dosage, Dr. Bhatt said that hypertension risk increases with higher GC doses, as the U.K. study indicates, and usually subsides when patients stop using GCs.

"Whether the observed dose association is causal or influenced by the underlying disease severity, our results suggest we should be vigilant in patients on all doses of GC, especially higher doses," Ms. Costello added.

In regard to using drugs that are less cardiotoxic than GCs, Dr. Bhatt said that there are clinical scenarios in which GC therapy is the best choice, so just switching to nonsteroidal drugs is no panacea.

The study was supported by the Centre for Epidemiology Versus Arthritis and by the National Institute for Health Research Manchester Biomedical Research Centre. Coauthor William G. Dixon, PhD, has received consultancy fees from Google and Bayer unrelated to this study. Dr. Bhatt has disclosed no relevant financial relationships.

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patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Studies: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

Gastrointestinal Perforations

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

MTX-controlled Studies: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

Thrombosis

Placebo-controlled Studies: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Studies: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled studies, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

Lipid Elevations

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled studies, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

Creatine Phosphokinase Elevations

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical studies, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

Lymphopenia

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

Anemia

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors

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

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The limited human data on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the maximum recommended human dose (MRHD), respectively, resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at approximately 0.3 and 2 times the exposure at the MRHD. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the MRHD resulted in no maternal or developmental toxicity *[see Animal Data]*.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.3 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with upadacitinib, and for 6 days (approximately 10 half-lives) after the last dose.

Data

Animal Data

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Pediatric Use

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

Geriatric Use

Of the 4381 patients treated in the five Phase 3 clinical studies, a total of 906 rheumatoid arthritis patients were 65 years of age or older, including 146 patients 75 years and older. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of overall adverse events in the elderly.

Renal Impairment

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

Hepatic Impairment

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

PATIENT COUNSELING INFORMATION

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

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions]*.

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ and in some cases can be serious *[see Warnings and Precautions]*.

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers. Instruct patients to inform their healthcare provider if they have ever had any type of cancer *[see Warnings and Precautions]*.

Thrombosis

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

Laboratory Abnormalities

Inform patients that RINVOQ may affect certain lab tests, and that blood tests are required before and during RINVOQ treatment *[see Warnings and Precautions]*.

Pregnancy

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*. Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations]*.

Lactation

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

Administration

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

Manufactured by: AbbVie Ireland NL B.V., Sligo, Ireland

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LAB-3919 **MASTER**

US-RNQR-200534

abbvie

RINVOQ™ (rin-'vōk) (upadacitinib) extended-release tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

SERIOUS INFECTIONS

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

If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

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

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

MALIGNANCIES

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

THROMBOSIS

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

INDICATIONS AND USAGE

Rheumatoid Arthritis

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were reported with RINVOQ.

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

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

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with RINVOQ. Interrupt RINVOQ if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with RINVOQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ may be resumed once the infection is controlled.

Tuberculosis

Patients should be screened for tuberculosis (TB) before starting RINVOQ therapy. RINVOQ should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of RINVOQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

Monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical studies with RINVOQ *[see Adverse Reactions]*. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 studies of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

Malignancy

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

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Thrombosis

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

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

Gastrointestinal Perforations

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

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

Laboratory Parameters

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3).

Lymphopenia

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

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ clinical studies.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL).

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol *[see Adverse Reactions]*. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Patients should be monitored 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo.

Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations]*.

Vaccination

Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines.

ADVERSE REACTIONS

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

- Serious Infections *[see Warnings and Precautions]*
- Malignancy *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Gastrointestinal Perforations *[see Warnings and Precautions]*
- Laboratory Parameters *[see Warnings and Precautions]*

Clinical Trials Experience

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

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the Phase 3 clinical studies of whom 2806 were exposed for at least one year.

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the study design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In studies RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

Table 1: Adverse Reactions Reported in greater than or equal to 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Studies

Adverse Reaction	Placebo n=1042 (%)	RINVOQ 15 mg n=1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

Placebo-controlled Studies: Studies RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Studies RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), upadacitinib 30 mg (n=384). Study RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling studies RA-III and RA-V.

MTX-controlled Studies: Studies RA-I and RA-II were integrated to represent safety through 12/14 weeks for MTX (n=530), RINVOQ 15 mg (n=534), and upadacitinib 30 mg (n=529).

12-Month Exposure Dataset: Studies RA-I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n=1213) and upadacitinib 30 mg (n=1203).

Exposure adjusted incidence rates were adjusted by study for all the adverse events reported in this section.

Specific Adverse Reactions

Infections

Placebo-controlled Studies: In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Studies: Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

Serious Infections

Placebo-controlled Studies: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Studies: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

Tuberculosis

Placebo-controlled Studies and MTX-controlled Studies: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

Opportunistic Infections (excluding tuberculosis)

Placebo-controlled Studies: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Studies: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

Malignancy

Placebo-controlled Studies: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100

RINVOQ™
upadacitinib 15mg tablets

IMPORTANT SAFETY INFORMATION[2]

SERIOUS INFECTIONS

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

Reported infections include:

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent infection prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Carefully consider the risks and benefits of treatment with RINVOQ prior to initiating therapy in patients with chronic or recurrent infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MALIGNANCY

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

THROMBOSIS

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

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in clinical studies with RINVOQ, although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with nonsteroidal anti-inflammatory drugs (NSAIDs). RINVOQ should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation.

LABORATORY ABNORMALITIES

Neutropenia
Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm^3. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia
Absolute lymphocyte counts (ALC) <500 cells/mm^3 were reported in RINVOQ clinical studies. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Anemia
Decreases in hemoglobin levels to <8 g/dL were reported in RINVOQ clinical studies. Treatment should not be initiated or should be interrupted in patients with hemoglobin levels <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

Lipids
Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Manage patients according to clinical guidelines for the management of hyperlipidemia. Evaluate 12 weeks after initiation of treatment and thereafter according to the clinical guidelines for hyperlipidemia.

Liver enzyme elevations
Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo. Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

EMBRYO-FETAL TOXICITY

Based on animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose. Verify pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ.

VACCINATION

Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, patients should be brought up to date on all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines.

LACTATION

There are no data on the presence of RINVOQ in human milk, the effects on the breastfed infant, or the effects on milk production. Available data in animals have shown the excretion of RINVOQ in milk. Advise patients that breastfeeding is not recommended during treatment with RINVOQ and for 6 days after the last dose.

HEPATIC IMPAIRMENT

RINVOQ is not recommended in patients with severe hepatic impairment.

ADVERSE REACTIONS

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

References: 1. Cohen SB, van Vollenhoven R, Curtis JR, et al. Safety profile of upadacitinib up to 3 years of exposure in patients with rheumatoid arthritis. Poster presented at: The European Congress of Rheumatology; June 3-6, 2020. E-Congress. **2.** RINVOQ [package insert]. North Chicago, IL: AbbVie Inc; 2020. **3**. Data on file, AbbVie Inc. Payer-reported lives. April 2020. **4.** Data on file, AbbVie Inc. ABVRRTI68885.

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

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Now with ~3.5 years maximum and 2 years median long-term exposure safety data[1]

RINVOQ™ upadacitinib 15mg tablets

For moderate to severe rheumatoid arthritis (RA) in adult MTX-IR patients[2]

EXCEPTIONAL ACCESS IS ALREADY HERE
RINVOQ HAS ACHIEVED
~95% PREFERRED COMMERCIAL COVERAGE[3*†]

National commercial coverage as of April 2020[3]

DEFY EXPECTATIONS

CHALLENGE TREATMENT GOALS IN RA

RINVOQ is a once-daily oral JAK inhibitor that met all primary (ACR20 or ACR50 at Week 12 or 14) and ranked secondary endpoints in 5 clinical trials.[2,4,a,b]

✓ Head-to-Head Trial Results

Superiority data evaluating ACR50, HAQ-DI, and pain reduction in RINVOQ + MTX vs a TNFi + MTX at Week 12
[ranked secondary endpoints in SELECT-COMPARE][2,4,a,b]

✓ Remission, Even Without MTX

DAS28-CRP<2.6‡ evaluated at Week 12 or 14
[ranked secondary endpoint in SELECT-COMPARE and SELECT-MONOTHERAPY][2,4,a,b]

‡Does not mean drug-free remission or complete absence of disease activity

✓ Radiographic Inhibition, Even Without MTX

ΔmTSS measured at Week 24 or 26
[ranked secondary endpoint in SELECT-COMPARE and SELECT-EARLY][2,4,a,b]

RINVOQ is not indicated for MTX-naïve patients

✓ Safety Data From 5 Robust Phase 3 Trials

>4350 patients across treatment arms, >4500 patient-years, ~3.5 years maximum exposure (median 2 years) to RINVOQ 15 mg[1,2,a-d]

LONG-TERM DATA

✓ All with the commitment to exceptional access and patient support from AbbVie.

Explore study results, including superiority data, at

RinvoqHCP.com

*Formulary definitions: Access means the product is covered and not NDC blocked. Restrictions may apply. Preferred/Step 1 means the product is placed on the plan's preferred formulary. Non-preferred products require a higher out-of-pocket cost or step edit, or are placed on a higher tier. Coverage means placed on formulary without a step edit through other biologics. For RINVOQ, this could include coverage on a non-preferred tier, which may result in a higher out-of pocket cost.

†Based on formulary status under the pharmacy benefit.

[a]Studied in adult patients with moderate to severe RA. [b]SELECT-EARLY (RA-I; MTX-naïve) [primary endpoint at Week 12: ACR50 response vs MTX, select ranked secondary endpoint at Week 24: ΔmTSS vs MTX]; SELECT-MONOTHERAPY (RA-II; MTX-IR) [primary endpoint at Week 14: ACR20 response vs MTX, select ranked secondary endpoint at Week 14: DAS28-CRP<2.6 vs MTX]; SELECT-NEXT (RA-III; csDMARD-IR) [RINVOQ + csDMARD; primary endpoint at Week 12: ACR20 response vs placebo + csDMARD]; SELECT-COMPARE (RA-IV; MTX-IR) [RINVOQ + MTX; primary endpoint at Week 12: ACR20 response vs placebo + MTX, select ranked secondary endpoints at Week 12: DAS28-CRP<2.6 vs placebo + MTX, HAQ-DI vs placebo + MTX, ACR50 response vs a TNFi + MTX, HAQ-DI vs a TNFi + MTX, pain reduction vs a TNFi + MTX; ΔmTSS vs placebo + MTX at Week 26]; SELECT-BEYOND (RA-V; bDMARD-IR) [RINVOQ + csDMARD; primary endpoint at Week 12: ACR20 response vs placebo + csDMARD]. [c]RINVOQ 15 mg; upadacitinib 30 mg; methotrexate; TNFi; placebo. [d]Long-term data as of 6/30/19.

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

INDICATION[2]

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

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

SAFETY CONSIDERATIONS[2]

SERIOUS INFECTIONS

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

MALIGNANCY

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

THROMBOSIS

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

OTHER SERIOUS ADVERSE REACTIONS

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

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

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

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