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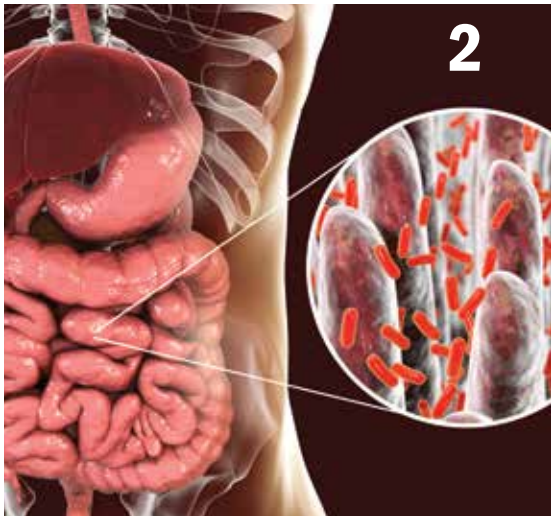
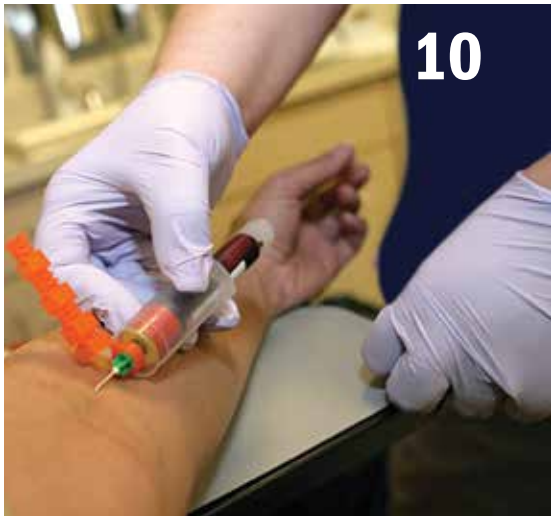
The RA Report

Top News Highlights





RA treatment responders show unique differences in gut microbiome

BY RICHARD MARK KIRKNER

FROM GENOME MEDICINE

The gut microbiome, previously shown to have an association with rheumatoid arthritis, may also provide signals of a patient's disease prognosis, researchers at the Mayo Clinic have reported.

Dr. Sung

"We found that the gut microbiome is linked to whether patients with RA improve in their clinical symptoms or not," cosenior author Jaeyun Sung, PhD, said in an interview. "We found features of the gut microbiome that linked to improvement, and we also put those features in a machine-learning model that can actually predict improvement at a follow-up visit." Dr. Sung is a computational biologist with Mayo Clinic's Center for Individualized Medicine in Rochester, Minn.

The retrospective, observational cohort study included 32 patients diagnosed with RA between 1988 and 2014 (Genome Med. 2021;13:149. doi: 10.1186/s13073-021-000957-0). The researchers performed meta-genome shotgun sequencing on 64 stool samples kept in a biobank and collected at two separate visits 6-12 months apart. Dr. Sung and colleagues observed significantly different microbiome traits between patients who eventually showed minimally clinically important improvement and those who didn't.

The study also provided a proof of concept for using machine-learning technology to analyze the gut microbiome to predict the course of the disease, Dr. Sung said.

Cosenior author John M. Davis III, MD, a clinical rheumatologist and rheumatology research chair of the Mayo Clinic, noted that their own previous study had confirmed dysbiosis in people with RA when compared with controls (Genome Med. 2016;8:43. doi: 10.1186/s13073-016-0299-7). "We had some preliminary insight that it may be linked to some extent to the disease state and maybe treatments," Dr. Davis said. "So that led us to hypothesize that there may be an association between the gut microbiome and response to treatment or disease activity over time."

Dr. Davis

The study found that age was the dominant factor in determining variations in the gut microbiome composition, but the next prevailing factor was minimum clinically important improvement status, which 12 of the 32 study participants achieved at their follow-up visits. At baseline, all patients were on some type of treatment – either biologic or conventional disease-modifying antirheumatic drugs (DMARDs, 46.9% and 87.5%, respectively), or prednisone (46.9%).

Gut microbiome composition

The patients who achieved minimum clinically important improvement had an average decline in Clinical Disease Activity Index of 16.7 units (standard deviation, 12.8) versus a gain of 5.7 (SD, 8.9) in the remaining patients. The study found higher species-level alpha diversity and richness and higher beta diversity in the group that achieved minimum clinically important improvement, compared with those who did not.

They identified six microbial taxa as higher in abundance in the improved patients: Negativicutes (class); Selenomonadales (order); Prevotellaceae (family); *Coprococcus* (genus); *Bacteroides* sp. 3_1_19 (species); and *Bilophila* sp. 4_1_30 (species). In the patients who showed no improvement, *Eubacterium* sp. 3_1_31 (species) was found to be higher ($P < .05$). They also found 15 metabolic pathways that were differently abundant between the two groups at baseline.

Two things make this study different from other studies of the gut microbiome in RA, Dr. Sung said: It didn't have a control group, only

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MDedge

Gut microbiome influences response to methotrexate in new-onset RA patients

BY JEFF CRAVEN

FROM ARTHRITIS & RHEUMATOLOGY

The pretreatment gut microbiome can determine response to methotrexate therapy in patients with newly diagnosed rheumatoid arthritis, according to recent research published in Arthritis & Rheumatology.

About half of patients do not respond to methotrexate (MTX), despite it being a first-line therapy for RA, according to Alejandro Artacho of the Centro Superior de Investigación en Salud Pública in Valencia, Spain, and colleagues. In addition, there is currently no way to predict which patients will respond to MTX.

Dr. Taneja

The role of the microbiome in drug response for patients with RA "has been known since it was discovered in 1972 that sulfasalazine requires gut bacteria for its activity," Veena Taneja, PhD, a researcher and associate professor of immunology at the Mayo Clinic in Rochester, Minn., said in an interview. The microbiome and how it functions "needs to be explored as biomarkers as well as for treatment options for RA and other diseases," added Dr.

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RA patients, and it didn't evaluate a specific drug in RA patients.

"We're thinking beyond just drug or treatment, independent of prior treatment, independent of prior clinical measurements, independent of age, sex, and other factors, can we predict RA response just using the gut microbiome alone?" Dr. Sung said.

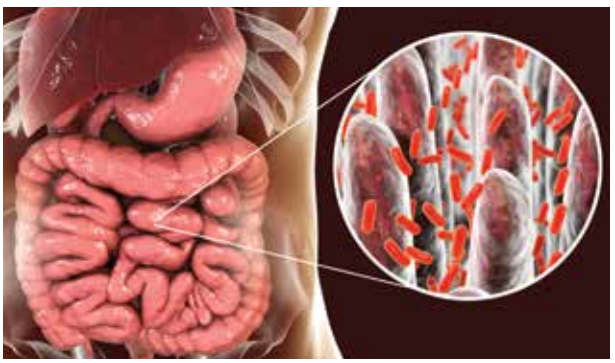
The study also showed that the microbiome may be a modifiable target for RA, Dr. Davis said.

"This research is attractive because it may complement medical treatment for RA if we can identify dietary modifications," he said. "Still, there's the question if probiotics or prebiotics can influence the gut. Can we modify the gut microbiome to further ameliorate the disease state? That's something I think is an open question that's specifically called out in our paper."

This study included patients with long-term disease, but the group's ongoing research is focusing on patients with earlier-stage RA, Dr. Davis said. "The next steps have to be in validating [the findings] in additional and external populations and looking at patients with very early disease where a lot of the decision-making is very active and happening in real time."

James T. Rosenbaum, MD, an ophthalmologist and rheumatologist at Oregon Health & Science University, Portland, acknowledged that this is the first study in RA to find an effect on the gut microbiome using the minimum clinically important improvement endpoint.

"It also raises a 'chicken-egg' dilemma," Dr. Rosenbaum said in an interview. "Did the patients improve and then their microbiome changed, or was the microbiome the first change that led to the clinical improvement? If the latter is correct, we potentially could alter the microbiome, for example, by diet, to treat rheumatic disease."



KATERYNA KON/SCIENCE SOURCE

He noted that studies with fecal transplants for ulcerative colitis support the therapeutic potential of microbiome modification. "But," he added, "we are still a long way from putting this in practice."

"The outcome is promising," Claudia Mauri, PhD, a professor of immunology at University College London, said of the study. "Obviously, if this can be repeated in a very large cohort of patients, it would give us the possibility to be able to, based on the composition of the microbiota, to predict who is going to respond to treatment or not."

Dr. Rosenbaum

Dr. Mauri

She noted that, while RA has a broader array of available treatments than other autoimmune diseases, some RA patients don't respond to their first biologic treatment. It would be beneficial to see who may not respond based on the microbiota, possibly allowing physicians to offer alternative second biologic agents.

Dr. Davis reported receiving research grants from Pfizer. Dr. Sung and other study coauthors have no financial relationships to disclose. Dr. Rosenbaum reported that the National Institutes of Health supports his research. Dr. Mauri has no financial relationships to disclose.

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Taneja, who was not involved with the study.

Using 16S rRNA gene and shotgun metagenomic sequencing, the researchers evaluated whether the gut microbiome of a patient newly diagnosed with RA (NORA) influenced their response to MTX. The researchers extracted DNA from fecal samples in 26 patients from New York University Langone Medical Center, Lutheran Hospital, Staten Island, and Mount Sinai School of Medicine rheumatology clinics 48 hours prior to treatment with MTX and determined the bacterial taxa, operational taxonomic units (OTUs), and ribosomal sequence variants in each sample. These patients then received oral MTX with an average dose of 20 mg per week (range, 15-25 mg). The patients were grouped based on whether they responded (39%) or did not respond (61%) to MTX based on improvement of at least 1.8 in their Disease Activity Score in 28 joints (DAS28) after 4 months and no need to add a biologic.

Patients with a statistically significantly lower level of microbial diversity ($P < .05$) as measured by OTU level tended to respond better to MTX therapy. In patients who did not respond to MTX, there was a significantly higher abundance of Firmicutes, a significantly lower abundance of Bacteroidetes ($P < .05$), and a higher ratio of Firmicutes to Bacteroidetes.

There was also a consistent difference between abundance of gut microbial genes in patients who did not respond to MTX. "Taken together, these results indicate that the gut microbiome of NORA patients that respond favorably to MTX is distinct from that of MTX-NR, prompting us to hypothesize that the pretreatment microbiome could be used to predict clinical nonresponse," the researchers said.

Using machine learning, Mr. Artacho and colleagues developed a predictive model based on the initial training cohort of 26 patients to assess MTX response. When the researchers tested the model in a validation cohort of 21 patients, they found it correctly predicted 78% of MTX responders and 83.3% of patients who did not respond to MTX, with the percentage of correct predictions increasing "when considering only those patients with the highest probability score of belonging to either group."

In a separate set of 20 patients with RA who were prescribed either different conventional synthetic disease-modifying antirheumatic drugs or biologics or had not started any medications, the researchers' model could not predict clinical response, "suggesting that the potential clinical utility of the model is restricted to RA patients that are both drug naive and exposed directly to MTX, but not to other drugs."

Dr. Kriegel

"Our results open the possibility to rationally design microbiome-modulating strategies to improve oral absorption of MTX and its downstream immune effects, inform clinical decision-making or both," they said.

Clinical application

Dr. Taneja said the findings of the study are novel and intriguing. "The observations suggest a strong influence of [the] host's microbiome in response to MTX and in future may inform best treatment options for patients. The study speculates that certain microbial clades or microbes can be used to derive a favorable response in patients. This could explain why 'one drug fits all' does not apply in treatment for RA," she said.

The study is also a "step forward" in using the microbiome in regular clinical practice, she noted. "Since MTX is used as a first line of treatment and is one of the most affordable treatments for RA, the observations are definitely exciting."

In an interview, Martin Kriegel, MD, PhD, of the department of immunobiology at Yale University, New Haven, Conn., and chair of rheumatology and clinical immunology at the University of Münster (Germany), explained that the prediction model has the potential to one day be a tool for clinicians to predict MTX response in patients with RA. However, he noted the researchers did not test a functional link between MTX and gut microbes in vivo.

"It would be useful to test mechanistic effects of MTX on gut microbial communities in vitro and in vivo," he said. "In addition, it would be informative to apply the prediction model in other cohorts of RA with a different geographic background, possibly also a different duration of disease. If confirmed in a more heterogeneous group of patients, the tool could potentially be used in the clinic to tell some patients that they might not respond to MTX and therefore start therapy with another agent."

This study was funded by the National Institutes of Health, the Rheumatology Research Foundation, the Searle Scholars Program, various funds from the Spanish government, the UCSF Breakthrough Program for Rheumatoid Arthritis-related Research, and the Arthritis Foundation Center for Excellence. Four authors report consultancies and memberships on scientific advisory boards with pharmaceutical and biotechnology companies that do not overlap with the current study.

Dr. Taneja reported that her institution holds a patent for developing *Prevotella histicola* as an anti-inflammatory treatment, of which she is a coinventor. Evelo Biosciences is a licensee for the patent, and Dr. Taneja reported receiving research support from the company. Dr. Kriegel reported receiving salary, consulting fees, honoraria, or research funds from AbbVie, Bristol-Myers Squibb, Cell Applications, Eligo Bioscience, and Roche. He also holds a patent on the use of antibiotics and commensal vaccination to treat autoimmunity.

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Gene variant confirmed as strong predictor of interstitial lung disease in patients with RA

BY TED BOSWORTH

FROM THE EULAR 2021 CONGRESS

Patients with rheumatoid arthritis who carry a specific allele of the gene MUC5B have about double the risk of developing interstitial lung disease when compared with noncarriers, according to a large Finnish biobank study presented at the annual European Congress of Rheumatology.

"The risk difference [or carriers relative to noncarriers] started at about age 65, with a bigger difference [for] men than women," reported Antti Palomäki, MD, PhD, of the center for rheumatology and clinical immunology at Turku (Finland) University.

The gain-of-function MUC5B variant, which encodes mucin 5B, was first linked to RA-associated interstitial lung disease (ILD) more than 3 years ago (N Engl J Med. 2018;379:2209-19. doi: 10.1056/NEJMoa1801562). At that time, it was already a known genetic risk factor for idiopathic pulmonary fibrosis in the general population. The new data confirm the association in a longitudinal analysis of a large biobank and suggest the association might have clinical utility.

"This is not ready for clinical practice at the moment. We do not yet know whether we can change therapy to reduce risk," Dr. Palomäki said, adding "in the future we can look."

One question that might be asked in clinical studies using MUC5B as a tool to assess and modify risk of ILD in patients with RA is whether one therapy is better than another in avoiding or delaying development of lung fibrosis. Dr. Palomäki noted that biologics, for example, might be a more favorable choice in patients with RA who are at high risk of developing ILD.

The association of the MUC5B variant with increased ILD incidence in patients with RA was drawn from a data set known as FinnGen, a biobank collection of epidemiologic cohorts and hospital samples with genotypes of about 10% of the Finnish population. Follow-up extends to 46 years in some of these individuals.

> "This is not ready for clinical practice at the moment. We do not yet know whether we can change therapy to reduce risk."

When 248,400 individuals in this data set were evaluated, 5,534 had a diagnosis of RA. Of these, 178 (3.2%) developed ILD. About 20% of both those with and without RA were MUC5B variant carriers, meaning the remainder were not.

Sex and age factor into lifetime risk

In patients with RA, the lifetime rate of ILD among MUC5B variant carriers was 16.8% versus only 6.1% among noncarriers. This finding translated into a hazard ratio for ILD of 2.27 (95% confidence interval, 1.75–2.96) for variant carriers versus noncarriers.

The lifetime rate of ILD in patients with RA was greater in men versus women regardless of carrier status (18.5% vs. 8.5%). For women, the lifetime rate was lower for carriers, although the difference relative to female noncarriers was greater (14.5% vs. 4.7%).

ILD, whether in the general population or in patients with RA, is a disease of advancing age. When Dr. Palomäki showed a graph, the rise in ILD incidence did not start in any population, whether those with or without RA and regardless of carrier status, until about age 55. In those without RA and in noncarriers of the variant, ILD incidence remained low and began a discernible climb at around age 70.

Dr. Palomäki

In those who did not have RA but were positive for the variant, the rates rose more than twice as fast, particularly after age 70. In people who had RA but not the variant, the rate of ILD was greater than in patients who carried the variant without RA, starting the climb earlier and rising more steeply with age. In those with RA and the variant, the climb in ILD incidence rose rapidly after age 65 years even though the incidence remained fairly similar between all of these groups at age 60.

Putting the findings into context

The need to develop ways to prevent ILD in RA is urgent. ILD is one of the most common extra-articular manifestations of RA, developing in up to 60% of patients with RA in older age groups when evaluated with imaging, according to Dr. Palomäki. Although it develops into a clinically significant complication in only about 10% of these patients, ILD still is a significant cause of illness and death in elderly patients with RA.

In the 2018 study that first linked the MUC5B variant to RA-ILD, the investigators also found that the variant was associated with an increased likelihood of developing the

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RA-ILD raises mortality risk in older patients

BY HEIDI SPLETE

FROM RHEUMATOLOGY

Patients with rheumatoid arthritis–associated interstitial lung disease showed increases in overall mortality, respiratory mortality, and cancer mortality, compared with RA patients without interstitial lung disease, based on data from more than 500,000 patients in a nationwide cohort study.

RA-associated interstitial lung disease (RA-ILD) has been associated with worse survival rates as well as reduced quality of life, functional impairment, and increased health care use and costs, wrote Jeffrey A. Sparks, MD, of Brigham and Women's Hospital, Boston, and colleagues. However, data on the incidence and prevalence of RA-ILD have been inconsistent and large studies are lacking.

In a study published online in Rheumatology (2021 Jan 18. doi: 10.1093/rheumatology/keaa836/6104048), the researchers identified 509,787 RA patients aged 65 years and older from Medicare claims data. The average age of the patients was 72.6 years, and 76.2% were women.

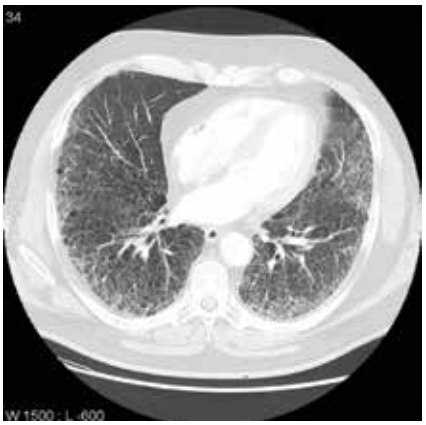
At baseline, 10,306 (2%) of the study population had RA-ILD, and 13,372 (2.7%) developed RA-ILD over an average of 3.8 years' follow-up per person (total of 1,873,127 person-years of follow-up). The overall incidence of RA-ILD was 7.14 per 1,000 person-years.

Overall mortality was significantly higher among RA-ILD patients than in those with RA alone in a multivariate analysis (38.7% vs. 20.7%; hazard ratio, 1.66).

In addition, RA-ILD was associated with an increased risk of respiratory mortality (HR, 4.39) and cancer mortality (HR, 1.56), compared with RA without ILD. For these hazard regression analyses, the researchers used Fine and Gray subdistribution HRs "to handle competing risks of alternative causes of mortality. For example, the risk of respiratory mortality for patients with RA-ILD, compared with RA without ILD also accounted for the competing risk of cardiovascular, cancer, infection and other types of mortality."

In another multivariate analysis, male gender, smoking, asthma, chronic obstructive pulmonary disorder, and medication use (specifically biologic disease-modifying antirheumatic drugs, targeted synthetic DMARDs, and glucocorticoids) were independently associated with increased incident RA-ILD at baseline. However, "the associations of RA-related medications with incident RA-ILD risk should be interpreted with caution since they may be explained by unmeasured factors, including RA disease activity, severity, comorbidities, and prior or concomitant medication use," the researchers noted.

The study findings were limited by several factors, including the lack of data on disease activity, disease duration, disease severity, and RA-related autoantibodies, the researchers noted. However, the results support data from previous studies and were strengthened by the large sample size and data on demographics and health care use.



COURTESY A.PROF FRANK GAILLARD, RADIOPAEDIA.ORG, RID: 12274

The study was supported by an investigator-initiated grant from Bristol-Myers Squibb (BMS). Lead author Dr. Sparks disclosed support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the Rheumatology Research Foundation, the Brigham Research Institute, and the R. Bruce and Joan M. Mickey Research Scholar Fund. He also disclosed serving as a consultant to BMS, and other companies for work unrelated to the current study. Other authors reported research funding from BMS, involvement in a clinical trial funded by Genentech and BMS, and receiving research support to Brigham and Women's Hospital for other studies from BMS and other companies.

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usual interstitial pneumonia type of ILD on imaging. David Schwartz, MD, professor of medicine, pulmonary sciences, and critical care and chair of the department of medicine at the University of Colorado at Denver, Aurora, was a senior author of that study. He said these findings build on the 2018 study.

"While the gain-of-function MUC5B promoter variant is important in predicting who will develop RA-ILD, these findings also suggest that MUC5B may be involved in the etiology of RA-ILD, at least for those with the MUC5B variant," he said.

"The study also raises the possibility that there are several subtypes of RA-ILD, and the subtype that is driven by MUC5B may respond differently to RA biologics or therapeutic agents to treat ILD," he added.

In the discussion following the presentation by Dr. Palomäki, others agreed with that statement, including Dr. Palomäki. He expressed interest in clinical studies comparing different classes of RA therapies for their relative impact on the risk of developing ILD.

Dr. Palomäki reported financial relationships with AbbVie, Merck, Pfizer, and Sanofi. Dr. Schwartz is the founder of Eleven P15, which is developing methods for early diagnosis and treatment of pulmonary fibrosis.

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Subanalysis of INBUILD trial suggests nintedanib slows RA-ILD progression

BY TED BOSWORTH

FROM THE EULAR 2021 CONGRESS

In a new subgroup analysis of a previously published multinational trial, the preservation of lung function with nintedanib (Ofev) was about the same in patients with interstitial lung disease related to rheumatoid arthritis (RA-ILD) as it was in patients with other etiologies, according to data presented at the annual European Congress of Rheumatology.

"There was no significant heterogeneity across any of several characteristics we evaluated," reported Clive Kelly, MBBS, of the Institute of Cellular Medicine at Newcastle University (England).

The INBUILD trial, which enrolled more than 600 patients in 15 countries with a range of fibrosing lung diseases, was published 2 years ago (N Engl J Med 2019;381:1718-27. doi: 10.1056/NEJMoa1908681). On the primary endpoint of rate of decline in forced vital capacity (FVC), the medians were –80.8 mL per year among those randomized to nintedanib and –187.8 mL per year ($P < .001$) on placebo.

The INBUILD study provided evidence that fibrosing lung diseases have a common pathobiologic mechanism that can be slowed by targeting intracellular kinases. Nintedanib inhibits several growth factor receptors as well as nonreceptor tyrosine kinases, but its exact mechanism for slowing fibrosing lung diseases remains unclear. Nintedanib received approvals from the FDA for systemic sclerosis–associated ILD in 2019 and for chronic fibrosing ILD with progressive phenotypes in 2020 after being initially approved for the treatment of idiopathic pulmonary fibrosis in 2014.

When asked for comment, Paul F. Dellaripa, MD, an associate professor of medicine in the division of rheumatology, immunology, and allergy at Harvard Medical School, Boston, indicated these data are helpful in considering strategies for RA patients with ILD, but he encouraged collaboration between joint and lung specialists.

"Antifibrotic agents for patients with progressive ILD in autoimmune diseases like RA is a welcome addition to our care of this challenging complication," Dr. Dellaripa said.

"It will be incumbent for rheumatologists to incorporate lung health as a critical part of patient care and work closely with pulmonologists to consider when to institute antifibrotic therapy in patients with ILD," he said.

Dr. Kelly

Details of subanalysis

In the RA-ILD subpopulation of 89 patients, there was no further decline in FVC from 24 weeks after randomization to the end of 52 weeks for those on nintedanib, but the decline remained steady over the full course of follow-up among those in the placebo group. At 52 weeks, the decline in the placebo group reached –200 mL. As a result, the between-group relative reduction in FVC at 52 weeks of 116.7 mL favoring nintedanib over placebo ($P < .037$) slightly exceeded the 107-mL reduction ($P < .001$) observed in the overall INBUILD study population.

Among other subgroups the investigators evaluated, outcomes with nintedanib did not differ when patients were split into groups with higher or lower baseline levels of high-sensitivity C-reactive protein. The same was true for those who were taking nonbiologic disease-modifying antirheumatic drugs or glucocorticoids.

However, for these latter analyses, Dr. Kelly said that the differences were based on few patients and cannot be considered conclusive.

The adverse event most closely associated with nintedanib in the RA-ILD population was diarrhea, just as in the overall study, and it was more than twice as frequent in the RA-ILD patients receiving the active therapy, compared with placebo (54.8% vs. 25.5%). Nausea was also more common (21.4% vs. 10.6%), and so was decreased appetite (11.9% vs. 2.1%) and weight reduction (9.5% vs. 2.1%).

Lung-related adverse events, such as bronchiolitis (21.4% vs. 17.0%) and dyspnea (11.9% vs. 10.6%), were only slightly more frequent in the nintedanib group. Nasopharyngitis (7.1% vs. 12.8%) was less common. Side effects leading to treatment discontinuation were higher on nintedanib (19.0% vs. 12.8%)

The RA-ILD subgroup represented 13.4% of those randomized in INBUILD. The mean time since diagnosis of RA was about 10 years. More than 60% were smokers or former smokers. At baseline, the mean FVC of predicted was 71%. More than 85% had a usual interstitial pneumonia (UIP) radiologic pattern.

Acute exacerbations and death were not evaluated in the RA-ILD subpopulation, but these were secondary endpoints in the published INBUILD study according to the presence or absence of a UIP-like fibrotic pattern. For the combined endpoint of acute exacerbation of ILD or death, the protection associated with nintedanib approached statistical significance for the population overall (odds ratio, 0.68; 95% confidence interval, 0.46-1.01) and reached significance for those with a UIP pattern (OR, 0.61; 95% CI, 0.38-0.98).

Dr. Kelly has financial relationships with multiple pharmaceutical companies, including Boehringer Ingelheim, which provided funding for INBUILD. Dr. Dellaripa reported financial relationships with Bristol-Myers Squibb and Genentech.

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Three Janus kinase inhibitors get boxed warnings and modified indications

BY JENNIFER LUBELL

The arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR) poses an increased risk of serious cardiac events such as heart attack or stroke, cancer, blood clots, and death, the Food and Drug Administration announced in September.

Manufacturers of this drug along with other Janus kinase (JAK) inhibitors baricitinib (Olumiant) and upadacitinib (Rinvoq) must update their boxed warnings to include information about these health risks. The FDA made the determination after new study data from Pfizer, which manufacturers Xeljanz, found an association between a lower dose of Xeljanz and increased risk of blood clots and death.

Dr. Furst

"Recommendations for healthcare professionals will include consideration of the benefits and risks for the individual patient prior to initiating or continuing therapy," the agency stated.

The FDA is limiting all approved uses of these three medications to patients who have not responded well to tumor necrosis factor (TNF) blockers to ensure their benefits outweigh their risks. Tofacitinib is indicated for rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis. Baricitinib and upadacitinib are approved only for RA. The FDA included baricitinib and upadacitinib in the warning because of the similar properties they share with Xeljanz, even though they haven't been studied as extensively.

"We believe this update will bring important clarity for healthcare plans on the risk/benefit profile of Xeljanz, which is a medicine informed by more clinical data than any other JAK inhibitor," Pfizer said in a statement.

Investigators for the ORAL Surveillance trial compared two doses of tofacitinib (5 mg twice daily and 10 mg twice daily) with TNF blockers in patients with rheumatoid arthritis who were aged 50 years or older with at least one additional cardiovascular risk factor.

For both dose regimens of tofacitinib, they found an increased risk of major adverse cardiovascular events (MACE), malignancies, thrombosis, and death compared with the TNF blocker regimen. In addition, rates of lung cancers and lymphomas were higher with tofacitinib. In trial data released earlier this year, Pfizer revealed that, when all dose regimens were combined, the tofacitinib group had a much higher incidence of adjudicated malignancies compared with the TNF blocker group (1.13 vs. 0.77 per 100 person-years; hazard ratio, 1.48; 95% confidence interval, 1.04-2.09).

Impact on clinical practice

Physicians treating patients who have rheumatoid arthritis with tofacitinib may initially decrease prescriptions following the FDA's drug safety communication, said Daniel E. Furst, MD, professor of medicine (emeritus) at the University of California, Los Angeles, adjunct professor at the University of Washington, Seattle, and a research professor at the University of Florence (Italy) – particularly those with a principal mechanism of action slightly different from that of tofacitinib, he added.

"Tofacitinib is principally a JAK 1,3 inhibitor at usual concentrations, whereas upadacitinib and baricitinib are JAK 1,2 inhibitors. Thus, I speculate that the tofacitinib prescriptions will go down more than the upadacitinib and baricitinib prescriptions," he said in an interview.

Some patients may also be worried about taking tofacitinib, particularly those with previous events or predisposing conditions, Dr. Furst noted.

"First and foremost, I think we need to actually look at the data in a publication rather than just an FDA statement before making huge changes in our practice," he advised.

"I am looking forward to the data finally being published ... It's interesting that the full data still isn't really out there beyond the press releases and an abstract. I think there's a lot more to learn about how these drugs work and who is really at risk for harmful events," said Alexis R. Ogdie, MD, MSCE, associate professor of medicine and epidemiology at the University of Pennsylvania, Philadelphia.

Pfizer's data also may be affecting FDA approvals of other JAK inhibitors. This past summer, AbbVie and Eli Lilly stated that the FDA's ongoing assessment of the safety trial was delaying the agency's decisions about expanding use of their respective drugs upadacitinib and baricitinib.

"I think many rheumatologists have already taken this information in, and begun to incorporate it into their discussions with their patients" since it has been over a year since the first public release of information about the ORAL Surveillance trial, said Arthur Kavanaugh, MD, professor of medicine at the University of California, San Diego. "I don't know that it will affect the approvals, but it will impact their labels."

The agency's decision corroborates an earlier 2019 warning about the increased risk of blood clots and of death in patients with ulcerative colitis taking 10 mg tofacitinib twice daily.

The FDA said that two other JAK inhibitors, ruxolitinib (Jakafi) and fedratinib (Inrebic), are not indicated for the treatment of arthritis and other inflammatory conditions, and so are not a part of the updates being required.

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Multiple comorbidities lower odds of controlling rheumatoid arthritis disease activity

BY TED BOSWORTH

FROM THE RHEUMATOLOGY RESEARCH FOUNDATION SUMMER SERIES

An increasing number of comorbidities in patients with rheumatoid arthritis correlates with a lower likelihood of reaching treatment targets, according to an analysis conducted with a series of large real-world datasets and presented in a symposium sponsored by the Rheumatology Research Foundation.

When compared with those with the lowest burden of comorbidity in one of these analyses, those with the highest had a nearly 50% lower likelihood (odds ratio, 0.54; 95% confidence interval, 0.34-0.85) of achieving low disease activity or remission, according to Bryant England, MD, PhD, assistant professor in the division of rheumatology at the University of Nebraska, Omaha.

"Patients with more comorbidities struggle to reach treatment targets," Dr. England said. In the treatment of RA, "we typically focus only on the joints, but these data suggest we need to begin to think more holistically about managing these patients."

Both the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) endorse a treat-to-target management approach in RA guidelines, but only a proportion of patients reach their targets, according to Dr. England. In his series of analyses, Dr. England has been exploring the role of comorbidities as one of the contributing factors.

Looking for real-world data, Dr. England evaluated comorbidities in the Veterans Affairs Rheumatoid Arthritis Registry, which has a male predominant population, the National Databank for Rheumatic Diseases, which is female predominant, the Truven Health Analytics MarketScan Database, and the Rheumatology Informatics System for Effectiveness Registry (RISE).

Comorbidities accrue more quickly in RA patients

All of these real-world data support the premise that comorbidities are higher in patients with RA than in those without, and show that the burden of comorbidities rises more quickly in patients with RA. For example, the average number of comorbidities in the MarketScan database of recently diagnosed RA patients was 2.6. Five years later, the average doubled to more than 5. For those without RA, the average at the baseline evaluation was 1.6 and remained below 3 at 5 years (Ann Rheum Dis. 2021;80:286-92. doi: 10.1136/annrheumdis-2020-218282).

For the burden of comorbidities in RA, Dr. England prefers the term "multimorbidity" because he believes it captures the interconnections of these chronic diseases, many of which trigger or exacerbate others. When he looked at health history 2 years before the RA diagnosis, multimorbidities were already somewhat higher, but he found that burden "takes off" in the peri-diagnostic period and climbs steeply thereafter.

"The data tell us that multimorbidity becomes more problematic throughout the RA disease course," said Dr. England, who published some of these data only a few weeks prior to his presentation (Arthritis Care Res. 2021 Aug 2. doi: 10.1002/acr.24762).

In one effort to evaluate how multimorbidity affects treatment choices and outcome, he selected patients with persistently active disease from the RISE registry, a group expected to be candidates for a treatment change or escalation. The data suggested patients with multimorbidity were less likely than were those without to receive a change of therapy in response to their active disease, but it also demonstrated that patients with multimorbidity were less likely to achieve remission or low disease activity even if the medications were changed.

Each comorbidity lowers odds of remission

When relative burden of comorbidities was assessed by RxRisk score, a validated medication-based measure of chronic disease that recognizes 46 categories of chronic conditions, there was about a 5% lower odds ratio for each RxRisk unit of increase in comorbidity. The relationship was consistent across various cohorts of patients evaluated, according to Dr. England.

When looking for patterns of comorbidities in these large datasets using machine learning, Dr. England reported that there were "striking" relationships between organ systems (Arthritis Rheumatol. 2020;72[suppl 10]: Abstract 0179). This included a pattern of cardiometabolic multimorbidity, cardiopulmonary multimorbidity, and mental health and chronic pain multimorbidity. Surprisingly, the same patterns could be identified in those with or without RA, but the prevalence differed.

"RA was closely associated with all of these different multimorbidity patterns, but the odds of having these patterns were one- to threefold greater," Dr. England reported.

"The multimorbidity pattern most closely associated with RA was mental health and chronic pain," he added, noting that the same results were observed across the datasets evaluated.

The implication of this work is that multimorbidity exerts an adverse effect on the course of RA and might be an appropriate target of

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Blood-based test aims to predict nonresponse to TNF inhibitors in patients with RA

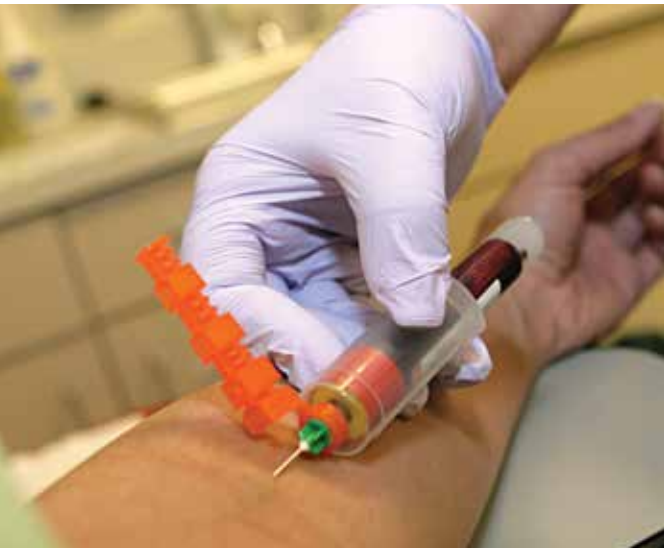
BY RICHARD MARK KIRKNER

FROM RHEUMATOLOGY AND THERAPY

A blood test that uses a patient's unique genetic signature has shown some ability to predict nonresponse to tumor necrosis factor inhibitors as treatment for rheumatoid arthritis, an observational clinical study has found, but the test's predictive accuracy was well below 100%.

The test is the blood-based molecular signature response classifier (MSRC) that uses RNA sequencing data based on 23 different biomarkers: 19 RNA transcripts and 4 clinical features. The clinical features are body mass index, gender, patient global assessment, and anticyclic citrullinated protein (anti-CCP) status.

The NETWORK-004 study, published in Rheumatology and Therapy (2021 Jun 19. doi: 10.1007/s40744-021-00330-y), was able to stratify patients who were likely to respond inadequately to TNFi therapy and could provide patient-specific information to guide therapy choice in RA patients regardless of whether they've already been on TNFi therapy. The study evaluated the MSRC test in 504 patients, 391 of whom were treatment naive.



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Avoiding 'fail first' approach

The idea behind the test is to circumvent the "fail first" approach in finding the right therapy for RA in an individual patient. While the test costs $4,995, Alif Saleh, chief executive officer of Scipher Medicine, which markets the test under the name PrismRA, said in a press release that it has the potential to reduce costs by $19,000 or more per patient per year by avoiding treatments that don't work. A previous study, which Scipher funded, reported that the test resulted in savings of $7,379 in per-patient costs of ineffective therapy (Rheumatol Ther. 2020;7:775-92. doi: 10.1007/s40744-020-00226-3). The same study reported a 25% decrease in costs for ineffective treatments for Medicare-eligible patients.

The price of RA drugs, particularly anti-TNF agents, is hefty and rising. GoodRx has reported that the price of RA drugs increased 92% from 2014 to 2019, and the prices for anti-TNF agents such as etanercept and adalimumab more than doubled in that period. Adalimumab can cost upwards of $84,000 per year while etanercept has a list price of around $72,000 a year. The pharmacy benefit manager WellDyne started covering the MSRC test in February.

Nehad Soloman, MD, a rheumatologist and internist at Midwestern University Arizona College of Osteo-

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therapies to improve RA outcomes. Although Dr. England called for better tools to measure multimorbidity and consider how it can be addressed systematically in RA patients with the intention of improving RA control, he believes this is an important direction of research.

"What our data show is that we need to begin to think more holistically about these other diseases in RA patients," he said.

Others support targeting of comorbidities

Vanessa L. Kronzer, MD, a rheumatology fellow at Mayo Clinic, Rochester, Minn., agreed. An author of a study that identified 11 comorbidities significantly associated with RA, either as conditions that predispose to RA or that commonly develop in patients with RA (Mayo Clin Proc. 2019;94:2488-98. doi: 10.1016/j.mayocp.2019.08.010), Dr. Kronzer has drawn the same conclusion in regard to targeting comorbidities in the RA patient.

"Based on mounting evidence that multimorbidity is associated with RA and RA disease activity, taking a broader view of the patient as a whole and his or her comorbidities may help us to not only predict RA but also achieve over disease-specific goals," Dr. Kronzer said in an interview.

"I suspect that certain comorbidities, perhaps depression as an example, may play a particularly strong role in perpetuating high RA disease activity," she added. She considers this a ripe area of study for improving clinical strategies in RA.

"Finding out which ones [perpetuate RA] and targeting them could be a reasonable approach to moving forward," Dr. Kronzer said.

Dr. England and Dr. Kronzer reported having no potential conflicts of interest.

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pathic Medicine in Glendale and a compensated NETWORK-004 investigator, said the MSRC test would be indicated for confirmed RA patients for whom rheumatologists are considering biologic agents, particularly TNFi drugs. "You wouldn't do it on an RA patient who's been on several different medications because it doesn't serve a purpose at that point," he said.

Dr. Soloman

The potential cost savings may not be the only reason to use the test, Dr. Soloman said. "You don't want to be dabbling with the wrong drug if there's another path you can try and save society some money as well as the time and energy it takes to monitor the patients – as well as the patient's pain," he said.

How the MSRC test works

The MSRC test detects a signal that's associated with a high or very high likelihood of inadequate response to TNFi therapies and indicates that the patient is unlikely to achieve low disease activity or remission with TNFi therapies. Response is defined as achieving 50% improvement in American College of Rheumatology response criteria (ACR50) at 6 months.

Test results are reported on a continuous 1-25 scale, explained Slava Akmaev, PhD, chief technology officer and head of therapeutics at Scipher. "The higher the score, the more likely the patient will have an inadequate response to TNFi therapies and be unable to reach low disease activity; the lower the score, the less likely the patient will have an inadequate response to TNFi therapies," he said. However, Dr. Akmaev noted that a low score does not ensure a positive response to TNFi therapies.

The MSRC test differs from the multibiomarker disease activity blood test (MBDA; marketed as Vectra by Myriad Genetics) in the number of biomarkers it measures: 19 RNA transcripts vs. 12 serum protein biomarkers in MBDA. The MBDA test is also intended to provide a quantitative, objective measurement of RA disease activity rather than to predict nonresponse to TNFi or other biologics. A number of studies have validated the MBDA test for predicting disease control in RA patients, but not necessarily response to TNFi therapy (BMC Rheumatol. 2019;3:3. doi: 10.1186/s41927-019-0071-x; J Rheumatol. 2019;46:555-63. doi: 10.3899/jrheum.180537).

The "high" category threshold of the MSRC test corresponds to an approximate 90% chance of inadequate response to TNFi therapy, or a 10% chance of responding. The "very high" category threshold corresponds to an approximate 95% chance of inadequate response to TNFi therapy, Dr. Akmaev said.

Dr. Akmaev

NETWORK-004 used area under the curve (AUC) to measure the accuracy of the MSRC test. An AUC of 1 represents 100% accuracy. Overall, the MSRC had an AUC of 0.64, or 64% accuracy of predicting patients unlikely to respond to TNFi therapy and to achieve ACR50 at 6 months, with an odds ratio of 4.1 (95% confidence interval, 2.0-8.3; $P = .0001$).

The predictive accuracy went up to 74% with ORs of 3.4-8.8 for additional endpoints at 3 and 6 months ($P < .01$). Among patients who had already been on TNFi therapy, the predictive accuracy was 83% and associated with ORs of 3.3-26.6 based on ACR, 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP), and Clinical Disease Activity Index (CDAI) metrics.

The investigators also performed an in-cohort cross-validation of the MSRC using baseline blood samples of 245 treatment-naive patients from the CERTAIN study, which yielded a 66% predictive accuracy for the ACR50 outcome at 6 months. Using the 19 RNA transcripts from the test, but not the clinical factors, the predictive accuracy was 62.5%. Using ACR70, CDAI, and DAS28 as measures for 6-month response, the cross-validation analysis of all 23 MSRC features yielded predictive accuracy of 64%-67%.

The study found significant differences in model scores between patients who did and did not have the molecular signal of nonresponse, and the proportion of patients who achieved low disease activity or remission at 6 months based on CDAI and DAS28-CRP measures was greater among those who lacked a molecular signature of nonresponse.

"Those who lack this signature can proceed with TNFi therapy and possibly achieve an increased response rate relative to the unstratified population," wrote lead study author Stanley B. Cohen, MD, and colleagues.

Daniel E. Furst, MD, emeritus professor at the University of California, Los Angeles, described the design of the NETWORK-004 study as "excellent," but said that it didn't overcome potential issues with the MSRC test itself. "The results unfortunately are great for group data but not for individuals, with a predictive area under the curve of 60% to 80%, it really is not that useful," he said. "Let's say you're a patient who's not doing well, and I do a test and it's positive; that still means that 20% of the time you will respond."

He also noted that he coauthored a paper that used decreases in DAS28 to predict nonresponse to certolizumab pegol plus methotrexate with 95% probability in the first 12 weeks of treatment (J Rheumatol. 2012;39:1326-33. doi: 10.3899/jrheum.111171). "That's closer to what we need," Dr. Furst said.

However, the MSRC test is a promising sign of where testing for predicting RA therapy is headed, he said. "We are steadily working toward genetic signatures that really are predictive on an individual basis," Dr. Furst said. "It's coming; it's just not here yet."

Dr. Furst had no relevant financial relationships to disclose. Dr. Soloman is a paid investigator and consultant to Scipher Medicine.

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Patients with RA on rituximab at risk for worse COVID-19 outcomes

BY SARA FREEMAN

FROM THE EULAR 2021 CONGRESS

Patients with rheumatoid arthritis who were using rituximab at the time of COVID-19 onset had a fourfold higher risk of being hospitalized, needing mechanical ventilation, or dying, compared with patients taking a tumor necrosis factor inhibitor (TNFi), according to a report given at the annual European Congress of Rheumatology.

The use of Janus kinase inhibitors (JAKi) also was associated with a twofold higher risk for these COVID-19 outcomes, said Jeffrey A. Sparks, MD, of Brigham and Women's Hospital and Harvard Medical School, Boston, in presenting the analysis from the COVID-19 Global Rheumatology Alliance (GRA) Physician Registry.

"The strong association of rituximab and JAK inhibitor use with poor COVID-19 outcomes highlights the prioritization of risk mitigation strategies for these patients," Dr. Sparks said at the meeting.

The full findings have now been published in Annals of the Rheumatic Diseases (2021 May 28. doi: 10.1136/annrheumdis-2021-220418).

Performing the analysis

As of April 12, 2021, the GRA Physician Registry contained the records of more than 15,000 patients. Dr. Sparks and associates limited their analysis to 2,869 patients with RA who had been treated with either a biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) at the time they were diagnosed with COVID-19.

"We wanted to limit it to a single disease and also limit it to drugs that are considered for that disease," Dr. Sparks explained in an interview.

"Because patients with rheumatoid arthritis are often treated sequentially, we wanted to further limit the analysis to patients who were on advanced therapies so that they were at a similar disease state, and also had the opportunity to receive advanced therapies."

Dr. Sparks

This approach hopefully minimizes the possibility of confounding by indication, Dr. Sparks said.

Most of the patients included in the analysis had received a TNFi (n = 1,388), and they were used as the control arm of the analysis. Outcomes associated with treatment with the other b/tsDMARDs, which included abatacept (n = 237), rituximab (n = 364), interleukin-6 inhibitors (IL-6i; n = 317), and JAKi (n = 563), were then compared with TNFi.

Baseline characteristics of patients were broadly similar across the groups. The mean age was 56.7 years and 80.8% of the study population was female. There were a few expected differences among users of rituximab versus TNFi, notably a higher percentage of patients with interstitial lung disease (11% vs. 1.4% of TNFi users) or cancer (7.4% vs. 0.9%) among patients treated with rituximab since it is commonly used in these patients, Dr. Sparks said.

"We did perform a sensitivity analysis where we restricted the population to not having ILD or cancer and we actually found really similar findings," he added.

Four COVID-19 outcomes assessed

The researchers used a four-point ordinal scale modeled after one set by the World Health Organization to assess four COVID-19 outcomes: not hospitalized, hospitalized without oxygenation, hospitalized with oxygenation or ventilation, and death.

Odds ratios (ORs) comparing rituximab to TNFi for these four COVID-19 outcomes were a respective 4.53, 2.87, 4.05, and 4.57. The ORs for JAKi versus TNFi were a respective 2.4, 1.55, 2.03, and 2.04.

"We found no consistent associations of abatacept or interleukin-6 inhibitors with COVID-19 severity, compared to TNF inhibitors," which is reassuring, Dr. Sparks said.

ORs for the four COVID-19 outcomes with abatacept were a respective 1.18, 1.12, 1.41, and 1.46, and for IL-6i were 0.84, 0.72, 0.75, and 1.13.

Rituximab use in patients with RA who develop COVID-19

So, should rituximab be stopped in patients with RA if they develop COVID-19? "This is an important question and one that would be decided on a case-by-case basis," Dr. Sparks said. "Of course, the drug has a very long half-life, so risk mitigation strategies are still of utmost importance," he added.

"I think everyone's a bit reticent to want to start rituximab in this environment, but it might also make me pause about starting a JAK inhibitor," Dr. Sparks added. "Given that this is a first finding, I'm not sure I would necessarily change patients who are doing well on these medications. I think what it really makes me want to do is to try to obviously vaccinate the patients on JAK inhibitors as they do have a short half-life."

More observational studies would be helpful, Dr. Sparks said, adding that "the most pressing need is to try to figure out how to protect our patients with rituximab."

The GRA Physician Registry is supported by the American College of Rheumatology and the European Alliance of Associations for Rheumatology. Dr. Sparks disclosed serving as a consultant for Bristol Myers Squibb, Gilead, Inova, Optum, and Pfizer for work unrelated to this study.

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Evidence grows for food as RA treatment

BY BRUCE JANCIN

FROM RWCS 2021

Patients with rheumatoid arthritis are often eager to try dietary interventions in an effort to improve their symptoms. For guidance, they turn to their rheumatologists, who typically can offer little in terms of concrete evidence-based recommendations. That's because their training didn't emphasize the role of nutrients in rheumatic diseases, the scientific evidence has historically been sketchy, and the topic of diet and disease is rife with fad diets, inflated Internet claims, and hucksterism.

But that's changing. Indeed, recent annual meetings of the American College of Rheumatology have featured randomized, controlled trials that bring welcome rigor to the field and provide findings of practical interest to clinicians and their patients, Orrin M. Troum, MD, said at the 2021 Rheumatology Winter Clinical Symposium.

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He highlighted some of this work, including positive randomized trials of the dietary supplements Biqi – a traditional Chinese herbal medicine – as well as turmeric, along with reported progress in efforts to design a palatable anti-inflammatory diet that favorably alters the gut microbiome and systemic metabolome while improving clinical outcomes in patients with RA.

Dr. Troum, a rheumatologist at the University of Southern California, Los Angeles, and in private practice in Santa Monica, described a typical patient encounter in his clinic that appeared to resonate with his audience from throughout the country: "You can tell people to take another medicine and they'll start shaking their head no before you're finished. But when you say there are natural supplements that can help you, they're saying 'Yes!' "

RA improvement on an ITIS diet

Many physicians recommend a Mediterranean-style diet, first popularized in the landmark Seven Countries Study launched by the late Dr. Ancel Keys. This familiar plant-based regimen emphasizes liberal consumption of extra-virgin olive oil, legumes, fruits and vegetables, whole grains, fish, nuts, and moderate alcohol intake, with very limited intake of red and processed meats, refined grains, and sugar. There is strong evidence that the Mediterranean diet is cardioprotective, which is relevant to patients with RA since they are known to be at elevated cardiovascular risk.

However, investigators at the University of California, San Diego, became convinced that the Mediterranean diet is lacking in key anti-inflammatory ingredients from other parts of the world. These include ginger, green tea, black pepper, turmeric, miso, flax seeds, and tahini, all of which are backed by evidence – from animal models and/or interventional diet studies in patients – that suggests beneficial effects in pain and joint swelling in RA. The researchers also suspected that certain vegetables embraced in the Mediterranean diet – notably eggplant, tomatoes, and potatoes – might be problematic for RA patients because they contain solanine, thought to increase intestinal permeability, which might have arthritogenic effects on the gut microbiome.

The investigators set out to develop an anti-inflammatory diet they call the ITIS diet, essentially tweaking the Mediterranean-style diet by incorporating these additions and subtractions (Contemp Clin Trials Commun. 2020 Jan 21 doi: 10.1016/j.conctc.2020.100524). Importantly, they designed the ITIS diet in conjunction with a multiracial local group of RA patients strongly enthusiastic about the potential for dietary interventions aimed at improving their symptoms. The patients provided feedback that enabled the investigators to fine-tune the anti-inflammatory diet so as to boost palatability and acceptance.

As an illustrative example of the ITIS diet, a typical day might start off with a homemade smoothie of parsley, pineapple, strawberries, and water, followed by a breakfast consisting of one or two corn tortillas spread with avocado, linseed oil, and sesame seeds, accompanied by green tea. Following a mid-morning

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snack of plain Greek-style yogurt, lunch might be a choice of a large salad, legumes with vegetables, or whole grains with vegetables. For the afternoon snack: four walnuts plus mango, banana, pear, papaya, apple, or pineapple. And for dinner, the options are vegetable soup and a protein; salad plus a protein; or miso soup, cooked vegetables, and a protein.

At the 2020 ACR annual meeting, Roxana Coras, MD, presented the positive findings of an open-label, pilot study of the ITIS diet in which 17 patients with active RA involving at least three tender and three swollen joints adopted the diet for 2 weeks (Arthritis Rheumatol. 2020;72[suppl 10]: Abstract 1994). The ITIS diet turned out to be not too much of a stretch for Southern California RA patients interested in dietary complementary and alternative medicine. Many had already adopted some elements of the anti-inflammatory diet. Dietary adherence in the study was good, as monitored in food logs and by mass spectrometry metabolic profiling of fecal and plasma samples.

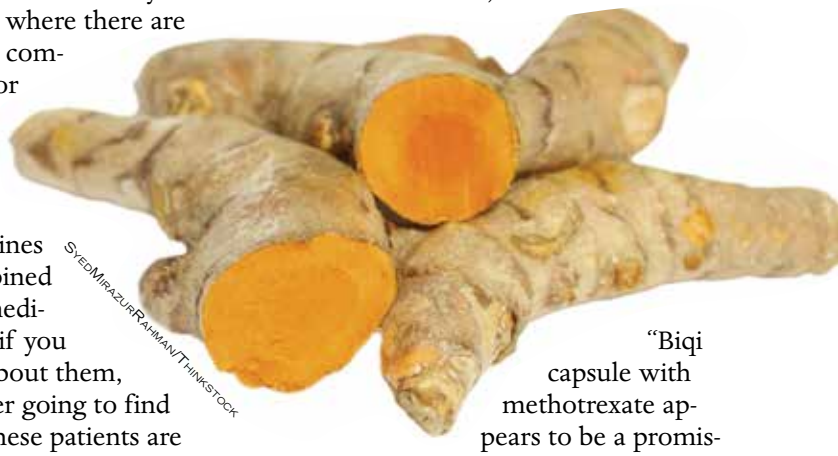
Eleven patients were categorized as responders to the anti-inflammatory diet as defined by at least a 50% improvement in pain scores from baseline to 2 weeks; six patients were nonresponders. In the overall study population, mean pain scores on a 0-10 visual analog scale improved from 3.9 to 2.45. Scores on the Clinical Disease Activity Index (CDAI) also improved significantly on the ITIS diet, from 29 to 12.7, reported Dr. Coras, a rheumatologist at the University of California, San Diego.

The mechanisms for the clinical improvement on the diet are under study. Significant differences in the gut microbiome and metabolome were seen between the responders and nonresponders. For example, Mollicutes were increased and Coriobacteriales decreased in clinical responders versus nonresponders. A significant increase in circulating levels of anti-inflammatory oxylipins was also seen in responders. Longer-term controlled studies of the ITIS diet are planned.

Biqi is big in China, gaining ground in the United States

Ayurvedic medicine in India and Chinese traditional herbal medicine have richly documented 4,500-year histories.

"It's so common in my neck of the woods, where there are large Asian communities, for Chinese or Korean or Japanese or Indian medicines to be combined with our medicines. And if you don't ask about them, you're never going to find out what these patients are taking," Dr. Troum said.



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If they're taking Biqi capsules, readily available on the Internet, be advised that there is randomized trial evidence to show that they're using an efficacious and safe herbal medicine for RA. In China, the combination of Biqi capsules and a conventional disease-modifying antirheumatic drug such as methotrexate is now widely used for treatment of RA. And at the 2019 ACR annual meeting, Runyue Huang, MD, of Guangzhou University of Chinese Medicine, presented the results of a 24-week, randomized, multicenter, open-label clinical trial in which 70 RA patients were assigned to methotrexate plus a 1.2-g Biqi capsule twice daily or to methotrexate plus leflunomide (Arava) at 20 mg/day (Arthritis Rheumatol. 2019;71[suppl 10]: Abstract 2385). The primary outcome – achievement of a 20% improvement in the ACR criteria, or ACR20 response, at week 24 – was achieved in 77% of the Biqi group, not significantly different from the 83% rate in the comparator group. However, the Biqi plus methotrexate group had significantly fewer adverse events and the combination was better tolerated than was leflunomide plus methotrexate.

In addition, a systematic review of earlier clinical trials concluded that Biqi in combination with methotrexate was more effective and had fewer adverse events than methotrexate alone (Exp Ther Med. 2018 Jun;15[6]:5221-30. doi: 10.3892/etm.2018.6121).

"Biqi capsule with methotrexate appears to be a promising combination for RA if you can rest assured that what's found in the Biqi capsule is exactly what they say. And that's the main issue: You don't really know what you're getting unless it's in a trial," Dr. Troum said.

American RA patients embrace turmeric

Turmeric has played a prominent role in Ayurvedic medicine for millennia. The most medicinally important component of turmeric root is curcumin, which has potent anti-inflammatory and antioxidant properties. Americans with RA have gotten on the bandwagon, as demonstrated in a survey of 291 patients with RA or psoriatic arthritis presented at ACR 2020 by investigators from the University of Central Florida, Orlando. Among the respondents, 37% reported having taken curcumin, with no predilection based upon age, gender, or diagnosis. Fifty-nine percent took their curcumin in the form of capsules, with the rest took it as an oil or powder. Fifty-four percent got their curcumin at a local store.

Thirty-six percent of curcumin users reported improvement

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Oral steroids plus proton pump inhibitors raise osteoporotic fracture risk

BY STEVE CIMINO

FROM ANNALS OF THE RHEUMATIC DISEASES

Rheumatoid arthritis patients who are on both oral glucocorticoids (GCs) and proton pump inhibitors (PPIs) have an increased risk of osteoporotic fractures, according to a retrospective study of RA patients in the United Kingdom.

"Considering the increasing life expectancies and high consumption of PPIs among elderly patients, fracture risk assessment could be considered when a patient with RA is co-prescribed oral GCs and PPIs," wrote Shahab Abtahi, MD, of Maastricht (Netherlands) University Medical Centre and colleagues. The study was published in Annals of the Rheumatic Diseases.

To determine if concomitant use of the two medications – both already associated with osteoporotic fractures – would lead to a notable increase in fracture risk, the researchers conducted a population-based cohort study of RA patients aged 50 years or older who were diagnosed during 1997-2017. Patient data was gathered via the Clinical Practice Research Datalink, a primary care database of millions of U.K. medical records.

Patients with a recent history of GC/PPI use or those with a previous osteoporotic fracture were excluded from the study. Osteoporotic fractures were defined as fractures of the hip, vertebrae, humerus, forearm, pelvis, or rib. The study population included 12,351 patients, roughly two-thirds of whom were women, with a mean age of 68 years. Of the population, 4,254 patients were concomitant users of oral GCs and PPIs, compared with 3,138 patients who were not on either medication.

> Fracture risk assessment could be considered when a patient with RA is co-prescribed oral GCs and PPIs.

Among all patients, 1,411 osteoporotic fractures occurred, 264 of which occurred in the concomitant users group. After adjustments for age and sex, patients on both medications had a higher risk of fracture (adjusted hazard ratio, 1.93; 95% confidence interval, 1.65-2.27), compared to patients on oral GCs alone (aHR, 1.34; 95% CI, 1.12-1.59) or PPIs alone (aHR, 1.32; 95% CI, 1.14-1.54). After full adjustment, concomitant users again had a higher risk of fracture (aHR, 1.60; 95% CI, 1.35-1.89).

Regarding specific types of breaks, the concomitant users had a notably higher risk of hip (aHR, 1.45; 95% CI, 1.11-1.91), vertebrae (aHR, 2.84; 95% CI, 1.87-4.32), pelvis (aHR, 2.47; 95% CI, 1.41-4.34), and rib fractures (aHR, 4.03; 95% CI, 2.13-7.63). No increased risk was found for either humerus or forearm fractures. The risk of fracture did not rise for concomitant users who had either increasing daily doses of PPI or a longer duration of use.

The authors noted their study's potential limitations, including having access to data on prescriptions only, not the actual use of medication, and a lack of information in the medical records regarding biologic therapies or certain indicators of RA disease activity. In addition, there was a likelihood that some patients who were improving might have stopped taking the drugs and lessened their risk of fracture, though the researchers attempted to account for this by "adjusting our analyses for six indicators of RA severity, including analgesics and [conventional synthetic disease-modifying antirheumatic drugs]."

Two of the authors reported receiving research grants and speakers' fees from various pharmaceutical companies. The others reported no conflicts of interest.

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in pain after going on the herbal supplement. Twenty-five percent reported reduced swelling, 23% had less stiffness, and 16% reported improvement in fatigue. Patients taking 200-1,000 mg/day reported significantly greater improvement in symptoms than that of those taking less than 200 mg/day. Onset of benefits was slow: Patients on curcumin for a year or longer reported greater symptomatic improvement than did those on the supplement for less time (Arthritis Rheumatol. 2020;72[suppl 10]: Abstract 1230).

Asked what he recommends to his RA patients who express interest in supplements aimed at achieving symptomatic improvement, Dr. Troum replied that he's comfortable suggesting curcumin capsules at 500 mg twice daily, which should be labeled as containing black pepper extract to aid in absorption. He also recommends fish oil both for its cardioprotective benefits and because of randomized trial evidence that it enhances the chances of achieving ACR remission in patients on conventional disease-modifying antirheumatic drugs.

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Vertebral fractures still a risk with low-dose oral glucocorticoids for rheumatoid arthritis

BY SARA FREEMAN

FROM RHEUMATOLOGY

Patients with rheumatoid arthritis currently being treated with low doses of oral glucocorticoids (GCs) had a 59% increased risk of sustaining a vertebral fracture when compared with past users, results of a retrospective cohort study have shown.

Although the overall risk of an osteoporotic fracture was not increased when comparing current and past GC users, with a hazard ratio of 1.14 (95% confidence interval, 0.98-1.33), the HR for sustaining a spinal fracture was 1.59 (95% CI, 1.11-2.29).

"Clinicians should be aware that, even in RA patients who receive low daily glucocorticoid doses, the risk of clinical vertebral fracture is increased," Shahab Abtahi, MD, of Maastricht (the Netherlands) University and coauthors reported in Rheumatology (2021 Jul 13. doi: 10.1093/rheumatology/keab548).

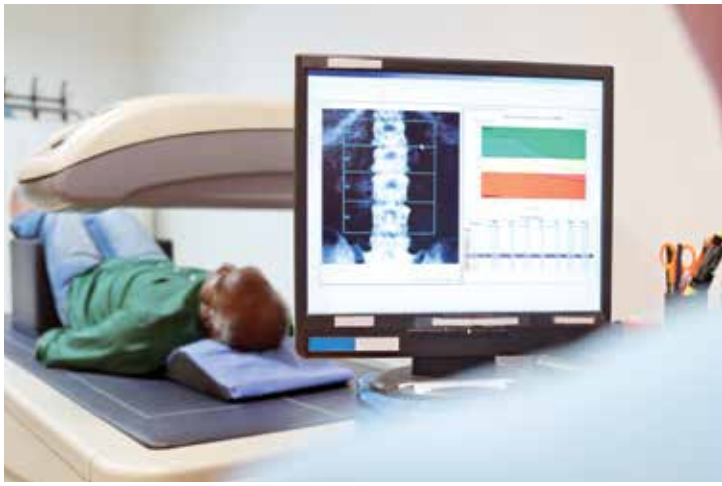
This is important considering around a quarter of RA patients are treated with GCs in the United Kingdom in accordance with European recommendations, they observed.

Conflicting randomized and observational findings on whether or not osteoporotic fractures might be linked to the use of low-dose GCs prompted Dr. Abtahi and associates to see if there were any signals in real-world data. To do so, they used data from one of the world's largest primary care databases – the Clinical Practice Research Datalink (CPRD), which consists of anonymized patient data from a network of primary care practices across the United Kingdom.

Altogether, the records of more than 15,000 patients with RA aged 50 years and older who were held in the CRPD between 1997 and 2017 were pulled for analysis, and just half (n = 7,039) were receiving or had received GC therapy. Low-dose GC therapy was defined as a prednisolone equivalent dose (PED) of 7.5 mg or less per day.

The use of low-dose GCs during three key time periods was considered: within the past 6 months (current users), within the past 7-12 months (recent users), and within the past year (past users).

The analyses involved time-dependent Cox proportional-hazards models to look for associations between GC use and all types of osteoporotic fracture, including the risk for incident hip, vertebral, humeral, forearm, pelvis, and rib fractures. They were adjusted for various lifestyle parameters, comorbidities, and the use of other medications.



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As might be expected, current GC doses even lower than 7.5 mg or less PED did not increase the chance of any osteoporotic fracture but there was an increased risk for some types with higher average daily doses, notably at the hip and pelvis, as well as the spine.

"Low-dose oral GC therapy was associated with an increased risk of clinical vertebral fracture, while the risk of other individual [osteoporotic] fracture sites was not increased," said the team, adding that the main results remained unchanged regardless of short- or long-term use.

"We know that vertebral fracture risk is markedly increased in RA, and it is well known that GC therapy in particular affects trabecular bone, which is abundantly present in lumbar vertebrae," Dr. Abtahi wrote.

"Therefore, we can hypothesize that the beneficial effect of low-dose GC therapy on suppressing the background inflammation of RA could probably be enough to offset its negative effect on bone synthesis in most fracture sites but not in vertebrae," they suggested.

The researchers lacked data on the disease activity of the patients or if they were being treated with biologic therapy. This means that confounding by disease severity might be an issue with only those with higher disease activity being treated with GCs and thus were at higher risk for fractures.

"Another limitation was a potential misclassification of exposure with oral GCs, as we had only prescribing information from CPRD, which is roughly two steps behind actual drug use by patients," they conceded. The average duration of GC use was estimated at 3.7 years, which is an indication of actual use.

Detection bias may also be involved with regard to vertebral fractures, with complaints of back pain potentially being discussed more often when prescribing GCs.

Dr. Abtahi and a coauthor disclosed receiving funding from several pharmaceutical companies unrelated to this study. All other coauthors had no conflicts of interest.

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Novel study links air pollution to increased risk of rheumatoid arthritis flares

BY TED BOSWORTH

FROM THE EULAR 2021 CONGRESS

In patients with rheumatoid arthritis, exposure to air pollution is associated with both elevated levels of C-reactive protein (CRP) and increased risk of arthritis flares, according to a novel longitudinal study presented at the annual European Congress of Rheumatology.

The data revealed "a striking association between air pollution and increased CRP levels and risk of an arthritis flare," reported first author Giovanni Adami, MD, DSc, of the rheumatology unit at the University of Verona (Italy).

The excess risk of elevated CRP and flares began "at very low levels of exposure, even those below commonly used thresholds for risk to human health," he added.

Study details

Researchers collected data on 888 patients with RA from numerous patient visits in the context of more than 13,000 air pollution records. The CRP levels and RA flares were evaluated in the context of air pollution monitoring that is performed on a daily basis at several sites in the city of Verona where the study was conducted. Verona is an industrial city in northern Italy that has high but variable levels of air pollution based on factory activity and weather conditions.

Patients with RA who provided clinical data for this study were matched by their proximity to specific air pollution monitoring sites. By linking CRP levels and disease activity to air pollution levels over multiple follow-up visits, the design allowed the RA study participants "to serve as their own controls," Dr. Adami explained.

At each patient visit during the study, CRP levels were measured and disease activity assessed. Patients were considered to have elevated CRP when levels were 5 mg/L or higher. The presence of an RA flare was defined by a 1.2-point increase or more in 28-joint Disease Activity Score using CRP (DAS28-CRP).

Both the CRP level and the presence or absence of a flare were evaluated in relationship to the patient's specific local air pollution levels in the prior 60 days.

Dr. Adami

Increased levels of CRP, a surrogate for inflammatory activity, and increased disease activity were both associated with elevated exposure to air pollutants prior to an office visit. These associations remained statistically significant when evaluated by specific air pollutants such as carbon monoxide (CO), nitrogen oxides (NO_2, NO), small particulate matter (PM10; particles ≤ 10 mcm), and ozone (O_3).

The relationship between increased exposure to air pollution contaminants and elevated CRP was supported by a dose effect. In the case of PM10, for example, the odds ratio of having elevated CRP was increased by only about 25% (OR, 1.25) when mean levels were 30 mcg/m^3 or lower in the period prior to the office visit. This rose incrementally for higher mean levels of PM10, reaching 70% (OR, 1.70) for levels > 50 mcg/m^3.

The researchers detected statistically significant differences in mean and area-under-the curve (AUC) values of most air pollutants in the 60 days prior to office visits when patients had a flare versus when disease activity was low. For example, the difference in mean and AUC levels in the period prior to a flare relative to a period with low disease activity was significant for CO ($P = .001$ for both) and NO and NO_2 ($P = .003$ for both), and O_3 ($P = .002$ and $P = .001$, respectively). For PM10, P values were .011 and .005, respectively.

"Remarkably, we found that the cumulative exposure to NO_2 in the 60 days preceding a flare was approximately 500 mcg/m^3 higher than the low disease activity visit, an exposure that equates to approximately 200 passively smoked cigarettes," Dr. Adami reported.

Trying to confirm causality of association

Dr. Adami's study is not the first study to link air pollution to risk of RA. Several have suggested that air pollution is a risk factor for developing joint disease, but a recently published study conducted in Kuwait associated greater disease activity with NO_2 and another air pollutant, sulfur dioxide (SO_2), although not CO, PM10, or O_3 (Int J Environ Res Public Health. 2020;17[2]:14).

A coauthor of that study, which evaluated pollution in regard to disease activity on DAS score, Adeeba Al-Herz, MD, a rheumatology consultant at Al-Amiri Hospital, Kuwait City, said in an interview, "We proved the correlation between them but not the causality."

However, she believes that this is an important area of inquiry.

"We are working now on another paper in which we studied a causal relationship between the two, meaning that we are evaluating whether SO_2 and NO_2 trigger RA activity," Dr. Al-Herz said. That study is now complete, and the manuscript is being written.

Dr. Adami believes that the evidence of an adverse effect on patients with RA is strong.

"In order to reduce the burden of RA, public and environmental health policy makers should aim to diminish gaseous and particulate matter emissions to a larger extent than currently recommended," he said.

In an interview after his presentation, Dr. Adami suggested that the

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Parental smoking in childhood linked to higher risk for onset of RA in adult women

BY RANDY DOTINGA

FROM ARTHRITIS & RHEUMATOLOGY

Childhood exposure to parental smoking appears to greatly boost the risk of confirmed cases of rheumatoid arthritis in adult women, although the overall rate is small, a new study reports. The findings, published Aug. 18, 2021, in Arthritis & Rheumatology (doi: 10.1002/art.41939), follows other evidence that early secondhand smoke exposure can trigger lifelong damage to the immune system.

"We estimated that there is 75% increased risk of adult seropositive RA due to the direct impact of childhood parental smoking," said study lead author and Brigham & Women's Hospital epidemiologist Kazuki Yoshida, MD, ScD, referring to an adjusted analysis conducted in the study. "Passive smoking is likely harmful throughout an individual's life course regarding rheumatoid arthritis but potentially more harmful during the childhood period."

> The findings are important because they drive home the importance of reducing cigarette smoke exposure to reduce risk of disease.

The researchers launched the study to fill an evidence gap, Dr. Yoshida said in an interview. "Active smoking is a well-established risk factor for RA. However, studies on passive smoking's impact on RA are sparse, and few studies had a well-characterized cohort of participants with comprehensive data of passive smoking during life course – in utero exposure, childhood exposure, adult exposure – and chart review–adjudicated RA outcomes."

The study authors retrospectively tracked 90,923 subjects who joined the Nurses' Health Study II in 1989 when they were aged 25-42. At the study's start, the average age of subjects was 34.5, 93% were White, and 98% were premenopausal. Almost two-thirds had never smoked themselves, and 65% said their

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risk of an inflammatory response and increases in arthritis flares from air pollution is not surprising. Previous studies have linked cigarette smoking to both.

"The mechanisms underlying the development of inflammation are very similar. Indeed, the toxic components contained in cigarette smoking are largely shared with diesel exhaust and fossil fuel combustion," he said.

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Although causality between air pollution and arthritis flares cannot be confirmed in these data, a basis for suspecting a causal relationship is supported by "plenty of in vitro and animal studies," according to Dr. Adami.

On the basis of these studies, several mechanisms have been postulated.

"As an example, exposure to air pollution can promote the activation of the bronchus-associated lymphoid tissue (BALT), which can trigger the activation of the transcription factor nuclear factor-kappaB," he said. This, in turn, can "lead to the secretion of proinflammatory cytokines, such as tumor necrosis factor–alpha and interleukin-1."

Another theory is that posttranslational modification of proteins in the lung, a process called citrullination, "can lead to production of autoantibodies known to have a pathogenic role in RA," he added.

Proving a causal relationship, however, is difficult.

"We certainly cannot conduct a randomized clinical trial on that and voluntarily expose some patients to pollution. Thus, we need to rely on observational data," Dr. Adami said.

Of strategies being considered to generate evidence of a causal relationship between pollution and the exacerbation of RA, "we certainly will try to study those patients that move from a highly polluted area to a greener zone and vice versa," he said. This will allow us "to explore what happens when the exposure to pollution changes dramatically in a short period of time."

Dr. Adami and Dr. Al-Herz report no potential conflicts of interest.

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parents had smoked during their childhoods.

Of the subjects, the researchers found that 532 were identified as having RA over a median follow-up period of 27.7 years. Two-thirds of those cases (n = 352) were confirmed as seropositive by clinical testing.

The study linked maternal smoking during pregnancy to confirmed RA in adulthood via a confounder-adjusted analysis (hazard ratio, 1.25; 95% confidence interval, 1.03-1.52), but the connection vanished after researchers adjusted their statistics to reflect possible influences by later exposures to smoke.

After adjustment for confounders, the study linked childhood exposure to parental smoking to a 41% in increase in risk of confirmed adulthood RA (HR, 1.41; 95% CI, 1.08-1.83). A controlled direct effect analysis boosted the excess risk to 75% (HR, 1.75; 95% CI, 1.03-2.98).

This analysis reveals that "childhood parental smoking seems to be associated with adult rheumatoid arthritis beyond what is explained by the fact that childhood passive smoking can promote personal smoking uptake, a known risk factor for rheumatoid arthritis," Dr. Yoshida said.

The overall rate of RA in the study population – roughly 0.6% – aligns with risk levels in the general population, he said. As a result, "the absolute risk increase may not be extremely high. But the concept that early life exposure may affect immunological health later in life is important."

Potential pathophysiological mechanisms

Why might parental smoking boost the risk of RA? Exposure to secondhand smoke may irritate the lungs and cause abnormal proteins to form, Dr. Yoshida said. "The immune system produces antibodies in an attempt to attack such abnormal proteins. This immune reaction can spread to other body sites and attack normal tissues, including the joints."

In addition, "smoking increases the risk of infections, which could in turn increase the risk of RA. Smoking is also known to result in epigenetic changes which could trigger RA in susceptible people," University of California, San Francisco, autoimmune disease epidemiologist Milena A. Gianfrancesco, PhD, MPH, said in an interview. She cowrote a commentary accompanying the new study (Arthritis Rheumatol. 2021 Aug 4. doi: 10.1002/art.41940).

Other studies have linked smoking exposure to autoimmune disorders. Earlier this year, researchers who tracked 79,806 French women reported at the EULAR 2021 annual meeting that they found a link between exposure to second-hand smoking during childhood or adulthood and higher rates of RA.

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Dr. Yoshida and colleagues noted their study's limitations, including the inability to track cases of RA in subjects up to the age when they entered the nurses research project. Also, only one questionnaire over the entire period of the Nurses' Health Study II asks subjects about whether they were exposed to secondhand smoke as adults.

The study also says nothing about whether a similar risk exists for males, and the nurse subjects are overwhelmingly White.

Still, Dr. Gianfrancesco praised the study and said it relies on extensive data and strong statistical methods. "The findings are important because they drive home the importance of reducing cigarette smoke exposure to reduce risk of disease," she said. "They highlight the need to not only focus on one's personal smoking habits, but also other sources of secondhand smoke exposure."

She added that children with a family history of RA or other autoimmune diseases are especially vulnerable to the effects of secondhand smoke because they may be more susceptible to developing the diseases themselves. "Rheumatologists and other health care providers should be sure to discuss the risks of smoking with their patients, as well as the risk of secondhand smoke," she said. "And parents should keep their children away from secondhand smoke in the home or other environments in which smoke is prevalent, such as the home of another caregiver or a workplace if the child accompanies their parent to work."

The study was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the Rheumatology Research Foundation, and the National Institutes of Health. The study and commentary authors, including Dr. Yoshida and Dr. Gianfrancesco, reported having no relevant disclosures.

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