SPOTLIGHT ON RESEARCH
Arthritis and Heart Disease
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WINTER 2014

Understanding the Risk

Patients with autoimmune diseases such as rheumatoid arthritis and lupus die earlier than matched controls, most often from cardiovascular events.

As if it weren't enough to live with the pain and challenges of arthritis, nearly half (47 percent) of the 52.5 million Americans with arthritis have other, often chronic, co-existing conditions. Heart disease, respiratory disorders, diabetes and stroke are the most prevalent of these conditions, also known as comorbidities.

Eleven million people with arthritis also have heart or cardiovascular disease (CVD), making CVD the most common comorbidity among arthritis patients. While many of these patients have a form of osteoarthritis (joint damage due to mechanical wear and tear), about three to four million have an autoimmune form of arthritis, such as, rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). In autoimmune forms of arthritis, the body's immune system mistakenly attacks its own healthy tissue (in this case, synovium in the joints) instead of the foreign cells it was designed to attack.

"To better understand the correlation between arthritis and CVD risk, investigators are focusing on patients with autoimmune forms of arthritis, particularly RA. These patients tend to get a more aggressive form of heart disease, with a disproportionate death risk when compared to the general population," explains John Hardin, MD, the Arthritis Foundation's Interim Vice President for Research. The Arthritis Foundation is currently funding several studies relating to how the disease mechanisms in arthritis impact the risk of heart disease.

Joan Bathon, MD, Director of the Division of Rheumatology at New York-Presbyterian Hospital/Columbia University Medical Center and Professor of Medicine at Columbia's College of Physicians and Surgeons, is a recognized authority on arthritis-related CVD risk. She is the principal investigator of several studies on the subject. "Patients with autoimmune diseases such as rheumatoid arthritis and lupus die earlier than matched controls, most often from cardiovascular events such as myocardial infarctions, strokes and heart failure," Dr. Bathon explains. "While accelerated risk of CVD in autoimmune patients may be explained in part by an apparent increase in conventional CVD risk factors compared to controls, this increase alone does not fully explain accelerated CVD in this group of patients. Something else is going on."

Dr. Bathon's team is currently enrolling RA patients with no CVD history to participate in a novel study to understand inflammation of their heart muscle. This study is unique because no one before has focused on the heart muscles of RA patients. "Using PET-CT scans," Dr. Bathon explains, "we are measuring inflammation in the heart and the blood vessels under the hypothesis that patients with RA may have some sort of low-grade inflammatory process that affects the muscle of their heart. And, like diabetes, inflammation might cause malfunction of small blood vessels in the heart resulting in lower blood flow to the heart muscle, giving it less nutrition and causing heart failure." Dr. Bathon currently has 85 people enrolled in the study and is seeking an additional 65.

In another study, Dr. Bathon and her team are seeking ways to identify RA patients at highest risk for atherosclerosis and myocardial infarction. Her team has singled out 50 proteins generally recognized in the medical community as associated with heart disease and/or with RA itself and is measuring these proteins in the RA patient samples to see if any of them correlate with severity of atherosclerosis in the heart (measured by coronary artery calcium). If the level of protein correlates with the level of coronary calcium, the protein could be used as a biomarker and can help identify RA patients at risk of developing aggressive CVD. Once identified, these patients can be treated more aggressively, and earlier, both to control the inflammation and to mitigate CVD risk.

In December 2012 Dr. Bathon and the Arthritis Foundation worked together to conduct a two-day conference at Columbia entitled *Enhanced Risk of Cardiovascular Disease in Patients with*

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Autoimmune Disorders. The goals of the conference were twofold: (1) to raise awareness among physicians of the heightened CVD risk in patients with autoimmunity in order to promote aggressive management of risk factors in this patient population; and (2) to develop an agenda for future research in this field of study. More than 100 cardiologists and rheumatologists attended the conference, an extraordinary event in that it brought together clinical scientists and basic scientists to collaborate on how the results of their studies could be translated into better patient care. The topic was also a hot one at the 2013 American College of Rheumatology convention in San Diego in November where more than 250 of the accepted abstracts at the meeting were on the subject of arthritis and the risk of CVD.

This issue of *Spotlight on Research* will explore research findings of three additional investigators working to better understand the link between autoimmunity and CVD and improving patient care—Dr. Anna Broder at Montefiore Medical Center, Dr. Jon Giles at Columbia University College of Physicians and Surgeons, and Dr. Jane Salmon at the Hospital for Special Surgery. During the course of their careers, all of the investigators featured in this issue were recognized for their work and pursued their ambitions with research grants from the Arthritis Foundation.

Anna R. Broder, MD, MSc

Assistant Professor, Department of Medicine (Rheumatology)
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Anna R. Broder, MD, MSc became interested in medicine after beginning her career as a data analyst and statistician. Currently Assistant Professor at Albert Einstein College of Medicine, Dr. Broder is a practicing rheumatologist, specializing in autoimmune forms of arthritis. She is also an investigator for the Einstein/Montefiore site of the Consortium of Rheumatology Researchers of North America, Inc. (CORRONA), a registry that collects information about patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Dr. Broder earned her medical degree at Robert Wood Johnson Medical School and a master's in clinical research at Einstein. Her early education focused on mathematics, which she pursued at Odessa University in the Ukraine and at Trinity College in Hartford. It is this background in mathematics and her practical experience as a rheumatologist that makes her a perfect match for a Pfizer-funded project she is currently undertaking at Montefiore Medical Center (MMC) in the Bronx.

"The patients I see in my rheumatology practice at MMC are among the highest CVD risk group in the nation," Dr. Broder said. This is mainly because MMC serves a large, ethnically diverse patient population and is located in New York City. Statistics show that black adults have higher premature mortality rates than white adults for all categories of CVD; and New York State also has a higher average age-adjusted CVD mortality rate than the rest of the nation. "We want to make sure that while treating the rheumatic disease, we don't overlook the cardiovascular health of our patients."

To support MMC physicians in the management of CVD risks in RA patients, Dr. Broder embarked on an 18-month multidisciplinary project to develop, implement, test, and disseminate a collaborative, physician-driven, integrated clinical decision support tool.

"This approach to collecting and organizing patient data is necessary today because patient care is very fragmented," Dr. Broder explains. "A patient may see a rheumatologist for arthritis, a cardiologist for heart disease, and other specialists as well. With a heavy patient load, administrative and often teaching responsibilities, physicians have limited time left for collaborating with colleagues on individual patients. This tool can serve as a valuable diagnostic and disease prevention resource for doctors."

For the first six months of the project, using the MMC electronic medical record (EMR) system, Dr. Broder worked with her MMC technical and medical colleagues and created a tool that can: (1) notify primary care and specialty providers if CVD risk assessment has not been performed for a patient with RA; (2) document a patient's CVD risks/risk scores; (3) alert providers when a patient is at increased CVD risk to promote collaboration and expedite RA patient care; and (4) support initiation of appropriate CVD risk reduction, lifestyle interventions and/or patient education.

Dr. Broder's tool is modeled after one designed to assess heart disease risk in patients with diabetes. It is based on the Framingham Risk Score, a system used to determine an individual's chances of developing CVD, considering factors such as age, gender, LDL cholesterol, HDL cholesterol, blood pressure, etc. "We designed the tool to be automatically populated with the information it requires from the patient's EMR," Dr. Broder

explained. "It is also capable of alerting providers if new lab tests need to be taken, or if other information is needed to update the tool and ensure an accurate evaluation." Once the necessary fields of the tool are populated, a physician can just click a button to access a patient's CVD risk assessment.

The next six months of the project will focus on piloting the tool at MMC and evaluating its impact on CVD screening and management of patients with RA. Dr. Broder will then gather the data from the pilot to demonstrate the benefits of EMR-based treatment in reducing CVD risk in RA patients. She plans to present her findings to other healthcare providers and health systems in New York State and nationwide via presentations at national meetings, manuscript publication, web presentations and a CME activity.

Dr. Broder's tool addresses one of two important considerations for optimizing patient care, i.e., the need for collaborative approach between different disciplines. The other major consideration is patient involvement in their own care—a critical factor in implementing successful interventions. To this end, Dr. Broder and her colleague, Nicole Jordan, MS, a research coordinator at Einstein, are planning to assemble a comprehensive patient education package.

Jon T. Giles, MD, MPH

Rheumatologist

Assistant Professor of Medicine, Division of Rheumatology
Columbia University College of Physicians and Surgeons

In his fourth year at Vanderbilt University School of Medicine in Tennessee, Jon T. Giles, MD, MPH did an outpatient rheumatology rotation and knew then what the focus of his medical career would be. "Most people come to rheumatology with an interest in immunology. I came primarily with an interest in musculoskeletal medicine," he said. As a fellow at John Hopkins Hospital in 2003, he was encouraged to pursue his interest in body composition and health outcomes in early rheumatoid arthritis (RA) with research grants from the American College of Rheumatology, National Institutes of Health, and the Arthritis Foundation. Also an epidemiologist, Dr. Giles is currently investigating the effect of RA on body composition and metabolic risk at Columbia University's College of Physicians and Surgeons.

To better understand why RA patients tend to develop cardiovascular disease (CVD) at a more accelerated rate than the general population, Dr. Giles and his colleagues are measuring fat and muscle tissue in an observational study. They are looking at how RA inflammation impacts the amount and quality of fat and muscle tissue, its distribution around the body, and how the observed changes might play a role in developing CVD. "For the last 10 years or so, we've been learning the magnitude of the problem," he said. "Now we are digging deeper so that we could actually intervene and improve outcomes for patients."

Using total body DXA imaging and computed tomography (CT) scanning, Dr. Giles and his team observed that RA patients had more visceral fat (deep, around the organs) and less muscle than the non-RA group. "Not only did we observe more visceral fat in RA patients, but the fat observed correlated strongly with cardiometabolic risk factors, inflammatory markers in the blood, and with atherosclerosis (hardening of the arteries) in a far more potent way than in the general population," Dr. Giles explained. The muscle observed in the RA group was also less dense than that of the general population and this lower muscle density, rather than amount of muscle, was a strong indicator of how much patients could do in terms of function and mobility.

"We are now enrolling patients to help us take this study a step further by providing needle aspirations of fat tissue from the abdomen to enable us to test them for markers of inflammation, such as, inflammatory proteins and cells," Dr. Giles added. The key to understanding the tissue differences is at the molecular level where cells are interacting and forming cytokines and other inflammatory proteins.

The scientific community has identified some of these proteins, IL-1, IL-6 and TNF-α, for example, as markers involved in the inflammatory process. But the mechanisms involved in these interactions are very complex and their study often presents confounding results. An example is the hormone adiponectin secreted by fat tissue. Dr. Giles and his colleagues found that, on the one hand, adiponectin acts as an anti-inflammatory agent in blood vessels, but, on the other hand, it appears to be a pro-inflammatory agent in the joints. It was also found that thin people with RA tend to have higher levels of adiponectin, and therefore, more joint erosion than heavier people with RA—the opposite of what you might expect. Dr. Giles and his team are currently seeking funding to study the

effects of a diet and exercise regimen on RA patients to determine how improving fitness would impact CVD in patients with RA.

"Finding out how and why these body composition changes occur in RA patients may help to discover interventions that can slow or stop the progression towards CVD," Dr. Giles explains. One possible answer is that chronic inflammation itself is responsible; perhaps reduced physical activity is to blame; medications to control the inflammation could play a role; or it could be some other immunologic features yet to be determined.

Jane E. Salmon, MD

Rheumatologist
Attending Physician,
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Professor of Medicine at Weill Cornell Medical College

Jane E. Salmon, MD is Director of the Lupus and APS Center of Excellence at the Hospital for Special Surgery (HSS) and one of the leading lupus experts in the world. For as long as she could remember, she wanted to be a scientist and make discoveries to improve the lives of patients, especially women. Her success is all the more remarkable since she trained at a time when women were subtly discouraged from following careers in academic medicine. She became the first woman enrolled in the Medical Scientist Training Program at Columbia University's College of Physicians and Surgeons. "Rheumatic diseases were interesting to me because there were so many unknowns," she said. "I found myself particularly drawn to systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), as they were diseases that afflict young women with whom I could identify."

Lupus is a systemic autoimmune disease that causes inflammation that can injure nearly every organ system in the body, including the skin, joints, kidneys, heart, lungs, and central nervous system. "Since the 1970s, outcomes for patients with lupus have improved markedly," Dr. Salmon said. "In those early days, many lupus patients would die within two years of their diagnosis from kidney failure or severe infections due to immunosuppression. Now patients with lupus live better and longer, but suffer from serious cardiovascular disease (CVD)."

In a study published in the November 19, 2003 edition of *The New England Journal of Medicine,* Dr. Salmon and her colleagues recruited 197 patients with lupus (mostly women) from the HSS Autoimmune Disease Registry. Each of these patients was matched with a control "partner"—someone similar in age, gender, and traditional risk factors for CVD, such as cholesterol, smoking, and blood pressure. The average age of the subjects in the study was 44 years. The subjects underwent carotid ultrasounds, echocardiograms, and an assessment for risk factors for CVD. They were evaluated with respect to their clinical features and disease treatment and had blood drawn for clinical and research laboratory tests.

The results of the study showed that the lupus patients had nearly three times the likelihood of having plaque in their carotid arteries, an indication of atherosclerosis (hardening of the arteries). Especially in the youngest age group, the prevalence of plaque was 5.6 times as high among lupus patients less than 40 years of age as among control subjects in this age group.

In a study conducted three years later with the same patients, Dr. Salmon and her colleagues found that not only did they have more prevalent plaque, but also that the rate of progression of their vascular disease was accelerated compared to a control group. "That the traditional risk factors associated with CVD did not predict this rapid progression of carotid artery plaque," Dr. Salmon said, "led us to conclude that the systemic inflammation of lupus itself is responsible." Another interesting finding was that the lupus patients who, at some point in their care, had received aggressive immunosuppressive treatment for their lupus had less plaque, suggesting that control of the inflammation might indeed retard progression of heart disease.

Dr. Salmon explains that: "In lupus patients, we have inhibited the inflammatory pathways and attenuated kidney damage, skin rash, arthritis and other clinical manifestations of this chronic rheumatic disease, but we have left behind 'smoldering' subclinical inflammation that may promote the development of heart disease." The mediators of vascular damage are not fully understood. Elucidation of the mechanisms of accelerated CVD in lupus will also help patients with other rheumatic diseases, and likely, patients with heart disease who do not suffer from rheumatic diseases.