Myocardial inflammation elevated in RA patients

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People with rheumatoid arthritis have an increased risk of heart failure even when controlling for coronary artery disease. Chronic myocarditis, or heart inflammation, is one suspected risk factor for cardiovascular disease (CVD) in this patient population. Two new studies measure the prevalence of myocardial inflammation in RA patients without known cardiovascular disease, assess how it is associated with high disease activity and show how disease-modifying therapy may decrease this type of inflammation, according to new research findings presented this week at the 2016 ACR/ARHP Annual Meeting in Washington.

Rheumatoid arthritis (RA) is a chronic disease that causes pain, stiffness, swelling, and limitation in the motion and function of multiple joints. Though joints are the principal body parts affected by RA, inflammation can develop in other organs as well. An estimated 1.3 million Americans have RA, and the disease typically affects women twice as often as men.

First, researchers at Columbia University in New York, N.Y., investigated the prevalence of myocardial inflammation in RA patients without known CVD, and evaluated how this inflammation was associated with disease-activity characteristics.

"Disease modifying anti-rheumatic drugs (DMARDs) have revolutionized the way we treat RA patients. Yet we continue to see increased incidence and mortality due to cardiovascular disease and heart failure in these patients compared to the general population which cannot be explained by traditional cardiovascular risk factors," said

Isabelle Amigues, MD, a rheumatology fellow at Columbia University Department of Medicine and a lead author of the study. "Biopsying the heart to confirm inflammation is invasive and expensive, but we now have very powerful imaging studies such as cardiac 18F-fluorodeoxyglucose positron emission-computed tomography (18-F-FDG-PET-CT) that can detect inflammation in the myocardium."

The study examined 118 RA patients without prior CVD events. Patients underwent cardiac 18-F-FDG-PET-CT scanning. Participants also underwent 3-D echocardiography to assess left ventricular (LV) mass, volumes, and systolic and diastolic function. Thirteen individuals without RA, frequency matched in age and gender to the RA group, were also studied to provide a cut-off value for normal versus abnormal. The investigators evaluated the relationship of the maximal standardized uptake value (SUVmax) for myocardial FDG uptake to the participants' disease activity scores.

The RA patients had a mean age of 55 years. Eighty-one percent were female, 37 percent were non-Hispanic white and 44 percent were Hispanic. The subjects' mean body-mass index was 28.5 and their median disease duration was seven years. In addition, 76 percent were positive for rheumatoid factor or anti-CCP, their mean DAS28 score was 3.78, and 28 percent had Clinical Disease Activity Index (CDAI) less than 10, consistent with low disease activity or remission. Forty-five of the RA patients used biologics, primarily TNF inhibitors (TNFi).

Median SUVmax was 12 percent higher in the RA patients compared to the controls. Higher BMI, and moderate-to-severe disease activity were positively associated with SUVmax in the RA patients. After adjusting for BMI and RA treatment, the mean SUVmax was 30 percent higher for the patients with moderate-to-severe disease activity compared with those who had low disease activity. Treatment with a non-TNFi biologic drug was associated with a 35 percent lower mean SUVmax compared to

RA patients either not on a biologic or on a TNFi. Age, gender, race, presence of diabetes, CRP and IL-6 levels, coronary flow reserve and coronary calcium score were not associated with SUVmax in the findings. SUVmax was not significantly associated with measures of left ventricular structure or function.

"This is the first report of a quantitative assessment of myocardial inflammation and the largest number of RA patients ever studied for myocardial inflammation," said Joan M. Bathon, MD, Director of Rheumatology at Columbia. "Previous studies were few, utilized cardiac magnetic resonance imaging in small numbers of patients, and relied on qualitative visual detection of gadolinium which cannot differentiate inflammation from edema, necrosis or fibrosis."

The correlation of myocardial inflammation with articular inflammation is compelling, as it suggests that treatment of joint inflammation could also help improve myocardial inflammation, Dr. Bathon said.

"Although we did not see an association of FDG uptake with abnormal heart structure or function in this cross-sectional analysis of RA patients with no clinical cardiovascular disease, it is possible that myocardial inflammation precedes any structural or functional changes. Further longitudinal studies are needed to assess the impact of baseline myocardial inflammation on adverse myocardial changes over time," she concluded.

In a second study, the researchers hypothesized that treatment with disease-modifying antirheumatic drugs (DMARDs) would improve subclinical myocardial inflammation in RA patients without clinical CVD, who are at higher risk of heart failure. Once again, cardiac 18-F-FDG-PET-CT imaging offered a more powerful, accurate way to detect and quantify the degree of inflammation in the heart. This type of imaging scan is used to assess cardiac sarcoidosis, it had not yet been

used in RA.

"Despite many advances in the field, the exact mechanisms that lead to heart failure in RA remain unclear," said Dr. Amigues. "We wanted to assess if patients with active RA but no overt cardiovascular disease had any degree of myocardial inflammation and whether it responded to increase in therapy."

RA patients who had no prior cardiovascular events and also had an inadequate response to methotrexate underwent a baseline cardiac 18-F-FDG-PET-CT scan. In a small, nested sub-study, patients underwent a repeat scan six months after initiation of step-up therapy. Non-RA controls underwent a baseline scan only. The researchers assessed myocardial FDG uptake, a measure of myocardial inflammation. RA participants also underwent 3-D echocardiography at baseline and six months to assess changes in left ventricular (LV) mass, volumes, and systolic and diastolic functions.

Twelve RA patients were enrolled in the nested sub-study, but only eight completed both scans. Twenty-five percent received triple therapy, and 75 percent received anti-TNF therapy with a background of methotrexate. The RA patients were 87.5 percent female, 62 percent seropositive, and had a mean age of 61±7.6 years and mean disease duration of 5±7 months. Thirteen controls were included. They were younger and there were fewer women. From the baseline to the second scan, mean DAS28-CRP, a measure of RA disease activity, decreased from 4.57±0.31 to 3.51±0.41. At the baseline scan, mean global myocardial standardized uptake values (SUV) max was significantly higher in the RA patients versus the controls, or 7.2 versus 3.4 units.

At the second scan, mean global myocardial SUV max decreased in the RA patients, and was not significantly different from the controls' measurements at baseline. Measures of left ventricular ejection fraction

and mass were in normal ranges for both groups. There were no significant changes in these measurements between the two scans for the RA patients.

The study's results show that while RA patients have a significantly higher myocardial FDG uptake, improving disease activity with DMARD therapy can improve this measurement. Next steps include conducting larger, long-term, longitudinal studies to examine how much myocardial inflammation contributes to heart failure in RA patients, said Dr. Bathon.

"Although this was a pilot study, we were excited to observe an improvement in myocardial inflammation with treatment of the patients' RA," she said. While longer, longer studies will help confirm and clarify these findings, "these are encouraging results for patients with RA. It supports the concept that appropriate treatment of the joint manifestations of their disease may also suppress and/or prevent myocardial inflammation and, potentially, the development of heart failure."

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