Biologic May Inhibit CVD, Depression in RA

BY DIANA MAHONEY

DESTIN, FLA. — The benefits of tumor necrosis factor blockade extend beyond the joints to the hearts and minds of rheumatoid arthritis patients, Dr. Iain McInnes reported at the Congress of Clinical Rheumatology.

Findings from two new studies suggest that anti-TNF treatment can inhibit the cytokine-induced chain of events that leads to the increased risk of cardiovascular disease and clinical depression in RA.

Along with lead investigator Dr. Mike J.L. Peters of VU University Medical Center in Amsterdam, Dr. McInnes and colleagues at the University of Glasgow (Scotland) have shown, for the first time, that anti-TNF-alpha therapy decreases circulating levels of the cardiac neurohormone N-terminal prohormone brain natriuretic peptide (NT-proBNP) in patients with rheumatoid arthritis (RA) who do not have evident heart failure.

Previously identified as a clinically relevant biomarker for heart failure, NT-proBNP is independently associated with cardiovascular risk in individuals with and without preexisting cardiovascular disease. Thus, the observed reduction in NT-proBNP suggests a "potential beneficial effect of [TNF-alpha] blockers with respect to vascular risk and ventricular function in rheumatoid arthritis," said Dr. McInnes.

The study measured serum NT-proBNP at baseline and after 16 weeks of biweekly adalimumab treatment in 171 consecutive RA patients without heart failure (Ann. Rheum. Dis. 2010 April 7 [doi:10.1136/ard.2009.119412]). After week 16, the investigators observed an approximately 18% reduction in NT-proBNP levels, providing biological evidence that TNF-alpha blockade does not worsen ventricular function in patients with RA who do not have prevalent heart failure, and supporting epidemiologic findings that indicate it may reduce overall cardiovascular risks in these patients, Dr. McInnes explained.

VITALS

Major Findings: TNF-alpha blockade decreases circulating levels of a clinically relevant biomarker for heart failure and alters the neurotransmitter pathway linked to depression in RA.

Data Source: Two observational studies.

Disclosures: Dr. McInnes has received research support or honoraria from Schering-Plough, Roche, Bristol-Myers Squibb Co., and Wyeth and has served as a consultant for Schering-Plough and Roche.

The results also add weight to the accumulating evidence that implicates TNF-alpha in the cardiovascular events associated with RA, and support the beneficial effect that blocking TNF-alpha has on surrogate vascular markers, he said.

In a separate study, Dr. McInnes and colleagues sought to assess the functional effects of anti-TNF-alpha therapy on the brains of depressed patients with RA, and determined that TNF-alpha blockade mediates altered serotonin transporter availability and induces an improvement in depression measures.

"This is critically important," Dr. McInnes stressed, referring to a 2006 report suggesting that the prevalence of major depressive disorder exceeds 40% and that of suicidal ideation is up to 11% in RA patients (Rheumatology [Oxford] 2006;45:1325-7).

Findings from earlier research have shown that proinflammatory cytokines can increase the density and activity of the serotonin transporter (SERT), a primary target for antidepressant therapy. On that basis, Dr. McInnes and his associates hypothesized that TNF blockade might be associated with altered SERT activity in RA patients, he said. They tested this hypothesis in a clinical, proof-of-concept study by measuring SERT density using SPECT (single-photon emission CT) in six patients with seropositive RA 2 weeks before the initiation of adalimumab therapy and 4 days after the last treatment, Dr. McInnes said.

After anti-TNF-alpha therapy, "there was a significant decrease in the [SERT] density in all of the patients." Along with that came overall improvements in physical and mental functioning, as measured by the Hamilton Rating Scale for Depression, the Social Functioning 36-item scale, the Hospital Anxiety and Depression Scale, and the composite 28 joint count Disease Activity Score, Dr. McInnes reported. ■

Atherogenic Profile Worsens With Polyarthritis Treatment

BY SARA FREEMAN

BIRMINGHAM, ENGLAND — Successful reduction of early inflammatory polyarthritis disease measures is accompanied by deterioration of the atherogenic profile, which potentially signals an increased risk of cardiovascular disease in an already at-risk population, judging from findings presented at the annual meeting of the British Society of Rheumatology.

'When you first meet your patient and you are reassured that their lipid levels are low, that is false reassurance.'

DR. MIRJAFARI

Results from a cardiovascular disease (CVD) subset analysis of data from the Norfolk Arthritis Register (NOAR) suggest that lipid parameters should be assessed and managed carefully in all patients with early arthritic disease. Such assessment and management should be done regardless of any ongoing inflammatory polyarthritis treatment.

"When we look at the HAQ [Health Assessment Questionnaire] scores, patients' disability and the disease severity are improving significantly over the first 2 years, but at the same time we see an overall worsening in their lipid profile," said clinical research fellow Dr. Hoda Mirjafari of the Arthritis Research UK Epidemiology Unit at the University of Manchester (England).

In her discussion of 2-year follow-up data on 223 patients, Dr. Mirjafari noted that although lipid levels initially seem to decrease in patients with early inflammatory polyarthritis, they creep back to normal levels over time.

"This is worrying on two counts," Dr. Mirjafari explained. "One is that when you first meet your patient and you are reassured that their lipid levels are low, that is false reassurance. Their true lipids, once their inflammatory disease is sorted out, are actually higher."

In addition, she said, conventional CV risk factor markers such as LDL and HDL cholesterol measures may not be good enough to track the worsening atherogenic profile and subsequent risk of atherosclerosis. A better measure is the atherogenic index, specifically the ratio of apolipoprotein B to apolipoprotein A-I. This is the only measure that can predict the likelihood of an atherosclerotic plaque's being present upon imaging of the carotid arteries.

Patients were recruited into the NOAR CVD substudy in 2004-2008 if they had evidence of early inflammatory polyarthritis and a disease duration shorter than 2 years. Information was collated at baseline and reassessed at 2 years on conventional CV risk factors (blood pressure, lipids, fasting glucose, height, and weight) and inflammatory polyarthritis risk factors (rheumatoid factor, HAQ, swollen and tender joint counts, and disease-modifying antirheumatic drug and steroid therapy).

Two-thirds (68%) of patients were female; the median age was 50 years, and the median symptom duration was 7 months. The median 28-joint count disease activity score based on C-reactive protein measures (DAS28-CRP) at baseline was 3.8. In all, 44% patients met American College of Rheumatology criteria for early inflammatory polyarthritis, and 48% were positive for rheumatoid factor. Only 5% of patients were receiving statin therapy; 23% were smokers, and 9% had a Framingham risk of CVD event greater than 20% at 10 years. One-fifth (22%) of patients had been exposed to steroids at baseline and 32% at 2 years, whereas 53% and 82%, respectively, had been treated with DMARDs.

Mean HAQ scores at baseline and at 2 years were 0.95 and 0.81, respectively. Mean swollen and tender joint counts were 3.73 at baseline, but decreased to 2.00 at 2 years. Although there was no great change in total cholesterol levels, LDL levels rose slightly and HDL levels decreased, and the atherogenic index increased substantially from a baseline value of 2.38 to 2.60 at 2 years. ■

Disclosures: *The NOAR is supported by a grant from Arthritis Research UK. Dr. Mirjafari reported no conflicts of interest.*

MY TAKE

Questions Remain About Statin Use in RA

Cardiovascular morbidity and mortality are obviously increasingly important in diseases like rheumatoid arthritis. Dr. Mirjafari made some interesting observations from some of the data from the Norfolk Arthritis Register. The findings so far leave a slightly counterintuitive impression. Here, evidence shows that the better we treat RA, not only the better the articular outcomes, but also the better the comorbidity outcomes. Yet the lipid profile seems to be deteriorating despite improvement in the disease.

What is a bit alarming is that this was a cohort of patients with relatively mild disease (only 48% were RF positive). It makes TRACE RA (Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Rheumatoid Arthritis) even more important as a study, so we can try and work out when it's the most appropriate time to use statins—not just with RA, but with a persistent inflammatory arthritis, even if it doesn't fulfill the American College of Rheumatology criteria.

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