Etanercept Cuts CRP in Metabolic Syndrome

BY MARY ANN MOON
Contributing Writer

Etanercept, a tumor necrosis factor–α antagonist usually used to treat inflammatory arthritis, decreased C-reactive protein levels and improved other inflammatory markers in patients with metabolic syndrome, reported Dr. L. Elizabeth Bernstein and her associates at Massachusetts General Hospital and Harvard Medical School, Boston.

Etanercept interferes with tumor necrosis factor–α's ability to bind with cell receptors, blocking the inflammatory response. The investigators examined the drug's effects on C-reactive protein (CRP) and other inflammatory markers associated with cardiovascular disease in 52 men and women with metabolic syndrome.

These subjects (mean age 46 years) had either hyperinsulinemia or impaired glucose tolerance; an elevated body mass index or a high waist-hip ratio; elevated serum triglycerides or low HDL cholesterol levels; and hypertension. All the subjects had elevated CRP levels at baseline, which was likely linked to an obesity-associated activation of the tumor necrosis factor system, since none had any other known inflammatory condition.

Half the subjects were randomly assigned to receive etanercept in two 25-mg subcutaneous injections weekly for 4 weeks, and the other half received placebo injections.

The findings 'suggest a novel and physiologically relevant approach to improve the increased inflammatory milieu associated with abdominal obesity.'

Etanercept reduced CRP levels by more than 2 mg/L, a 34% reduction within 4 weeks. Weight, nutritional status, and body composition remained unchanged, indicating that the drug acted independently of these factors to improve CRP, the researchers said (Arch. Intern. Med. 2006;166:902-8). At the same time, adiponectin levels rose significantly. Adiponectin, an adipocyte-derived cytokine that has anti-inflammatory and antiatherosclerotic properties, is decreased in obese people. Etanercept also decreased the subjects' markedly high levels of fibrinogen, a clotting factor and marker of inflammation and abnormal hemostasis. The drug also tended to reduce levels of interleukin-6 levels, another indicator of inflammation. It did not affect insulin sensitivity.

Etanercept was well tolerated in these subjects. However, they had been well screened before enrollment for contraindications to the drug, known to impair immune function in some patients. "Further studies with longer duration will be necessary to determine the safety" of etanercept in people with metabolic syndrome, the investigators noted.

The findings "suggest a novel and physiologically relevant approach to improve the increased inflammatory milieu associated with abdominal obesity" and metabolic syndrome. But additional studies are needed to investigate such a hypothesis. ■

Insulin Resistance in RA May Underlie Cardiovascular Risk

BY NANCY WALSH
New York Bureau

GLASGOW, SCOTLAND — High rates of insulin resistance among patients with rheumatoid arthritis may help explain these patients' increased risk for cardiovascular disease, according to a poster presented by Dr. George D. Kitas at the annual meeting of the British Society for Rheumatology.

Evidence has been increasing that suggests involvement of chronic inflammation in atherosclerosis and coronary heart disease in both rheumatoid arthritis (RA) patients and the general population, but the precise disease processes are not fully understood, Dr. Kitas noted.

Insulin resistance is strongly associated with systemic inflammation. Insulin itself is an anti-inflammatory hormone, the actions of which include suppression of proinflammatory transcription factors and adhesion molecules. It also has antioxidant properties and, in a rat model, suppresses cytokines including interleukin-1β, IL-6, and tumor necrosis factor.

Conversely, hypernutrition and the insulin-resistant state are proinflammatory, noted Dr. Kitas of the department of rheumatology, Dudley Group of Hospitals and the University of Birmingham, both in England.

"Evidence for this arises from observations that treatment of type 2 diabetes reduces C-reactive protein and macrophage chemotactic protein-1," he wrote. Moreover, diabetic ketoacidosis induces an inflammatory response that normalizes with insulin treatment.

To investigate the prevalence and clinical factors associated with insulin resistance, Dr. Kitas and his colleagues assessed 244 consecutive RA patients. A total of 70.5% were female, mean age was 61.6 years, and mean disease duration was 13.5 years.

Mean body mass index (BMI) was 27.5 kg/m^2. Mean levels of C-reactive protein (CRP) and erythrocyte sedimentation rate were 18.6 mg/L and 30 mm/hr, respectively.

Rheumatoid factor (RF) was positive in 70.5% of patients. A total of 6.6% already had a diagnosis of diabetes, compared with 2% of the United Kingdom population.

Insulin resistance was determined on the homeostasis model assessment (HOMA) index and the quantitative insulin sensitivity check index (QUICKI).

Among patients who did not have an established diagnosis of diabetes, 37.3% and 38.2% had abnormal findings on HOMA and QUICKI, respectively.

Among these patients with insulin resistance, systolic blood pressure, triglyceride and uric acid levels, and body mass index were significantly higher than in those with normal insulin function. CRP and RF titers also were higher, while high-density lipoprotein level was lower.

Logistic regression analysis found that higher BMI, RF titer, and uric acid level were independent predictors of insulin resistance, according to Dr. Kitas. Steroid use did not correlate with insulin resistance.

The association of elevated RF titer and insulin resistance has not previously been described, he noted. "A possible explanation for this may be that RF acts as a surrogate marker for cumulative inflammation or damage, or it may reflect metabolic or genetic processes influencing insulin sensitivity among RA patients."

According to Dr. Kitas, the study raises the following questions that require further investigation:

► Could improved disease control reduce insulin resistance?

► Would BMI reduction and increased exercise reduce insulin resistance?

► Do patients with RA and insulin resistance subsequently develop type 2 diabetes?

► What is the precise role of RF in insulin resistance?

► Will a reduction in insulin resistance ultimately reduce the cardiovascular disease risk in RA patients? ■

CVD Risk Dramatically Higher in Type 1 Diabetics: Intervene Early

BY SHERRY BOSCHERT
San Francisco Bureau

Major cardiovascular disease is four times more common in men and eight times more common in women with type 1 diabetes, compared with nondiabetic men and women, Sabita S. Soedamah-Muthu, Ph.D., reported.

Type 1 diabetes also dramatically increases risks for fatal cardiovascular disease, major coronary heart disease, stroke, coronary revascularization, and acute coronary events, even in the modern era of emphasis on intensive glycemic control, said Dr. Soedamah-Muthu of the Royal Free and University College, London.

The first large, controlled study to evaluate absolute and relative risks of both morbidity and mortality related to cardiovascular disease in type 1 diabetics found that absolute risk levels seen in the nondiabetic population by age 60 appear in men with type 1 diabetes around ages 45-50 years and even earlier in women, said Dr. Soedamah-Muthu and associates (Diabetes Care 2006;29:798-804).

The investigators analyzed data from the General Practice Research Database, a large primary-care database from a network of 603 practices. They compared data for 7,479 patients with type 1 diabetes with data for 38,116 nondiabetic control patients, with five controls matched to each diabetic patient by age and sex.

The risk for fatal cardiovascular disease was increased 6-fold in men and 12-fold in women with type 1 diabetes, compared with controls of the same sex. The risk for major coronary heart disease was quadrupled in men and 10 times higher in women with type 1 diabetes, compared with nondiabetic patients. Strokes, both fatal and nonfatal, were four times more common in men and five times more common in women with type 1 diabetes.

Coronary revascularizations were performed 5 times more often in men and 17 times more often in women with type 1 diabetes, compared with controls. The risk for acute coronary events tripled in men and was eight times higher in women with type 1 diabetes, compared with nondiabetic controls.

It is unclear how much of these increased risks might be explained by the long duration of glycemic exposure. The average duration of diabetes in the study was 15 years. The causes of higher risks in women also are unclear.

"Whatever its basis, the ongoing dramatic elevation in CVD [cardiovascular disease] risk in type 1 diabetic patients, especially diabetic women, needs to be emphasized to clinicians, as the relatively good lipid profile of type 1 diabetic patients without renal disease could lead to their CVD risk being underappreciated," Dr. Soedamah-Muthu wrote.

Clinicians should evaluate patients with type 1 diabetes for potential preventive interventions such as statin therapy starting at 45 years of age, possibly younger, the investigators suggested. Because traditional risk factors for cardiovascular disease may be less effective in identifying risk in diabetic than in nondiabetic patients, it might be reasonable to consider imaging to look for early cardiovascular disease in addition to measuring traditional risk factors in patients with type 1 diabetes, they added.

The absolute risk for cardiovascular disease at ages 45-55 was 11/1,000 person-years in men with type 1 diabetes and 4/1,000 person-years in male controls. In women aged 45-55 years, the absolute risk for cardiovascular disease was 10/1,000 person-years in those with type 1 diabetes and 1/1,000 person-years in controls. The hazard ratio for major cardiovascular disease among diabetics in that age group, compared with controls, was 3 for men and 10 for women.

The higher risks for cardiovascular disease in women could not be attributed to a greater propensity to diagnose or treat cardiovascular disease in diabetic women, the investigators said. ■