

Interferon Pathway May Lead to Biomarker of Lupus Severity

BY PATRICE WENDLING
Chicago Bureau

Activation of the interferon- α pathway identifies a subgroup of lupus erythematosus patients with distinct serologic features and more active disease, according to Kyriakos A. Kirou, M.D.

There is no consensus in the current literature regarding the most useful or accurate marker of lupus disease activity, thus the use of increased interferon-inducible gene expression as a potential biomarker of active disease could prove valuable to clinicians and researchers.

The investigators subjected freshly isolated peripheral blood mononuclear cells from 77 patients with systemic lupus erythematosus (SLE), 22 disease controls with either rheumatoid arthritis or inflammatory uveitis, and 28 healthy donors to real-time polymerase chain reaction for three genes (*PRKR*, *IFIT1*, and *IF144*) that are preferentially induced by interferon- α . The results were used to determine an IFN- α score for all participants.

SLE patients with a high IFN- α score had a significantly higher prevalence of renal disease, a greater num-

ber of American College of Rheumatology criteria for SLE, and a higher Systemic Lupus International Collaborating Clinics damage index (SDI) score than did patients with a low IFN- α score (*Arthritis Rheum.* 2005;52:1491-503).

Patients with high IFN- α scores also showed increased disease activity, as measured by lower serum C3 levels, hemoglobin levels, absolute lymphocyte counts, and albumin levels, and a higher anti-double-stranded DNA (dsDNA) titer, erythrocyte sedimentation rate, and SLE Disease Activity Index 2000 score.

"Our most striking data, and that which may provide us new clues regarding underlying disease mechanisms, came from analysis of the serologic profiles of the SLE patients," wrote Dr. Kirou and colleagues at the Hospital for Special Surgery in New York.

The investigators found that the presence of antibodies specific for RNA-binding protein (RBP), including Ro,

U1 ribonucleoprotein (RNP), and Sm, was significantly associated with a high IFN- α score.

Logistic regression analysis confirmed that the presence of renal disease, low complement levels, autoantibodies specific for RBP (but not anti-dsDNA or antiphospholipid autoantibodies), and higher SDI scores, all independently increased the likelihood of having a high IFN- α score.

"Activation of the IFN- α pathway could be an important mediator of the immune system alterations that confer tissue damage in SLE," the authors wrote.

Additionally, activation of the IFN- α pathway may also contribute to production of pathogenic autoantibodies by direct and indirect effects on B cells, resulting in differentiation and Ig class switching to IgG and IgA isotypes.

Prospective longitudinal studies are needed to assess the role of interferon-inducible genes in monitoring disease activity, they concluded. ■

'Activation of the IFN- α pathway could be an important mediator of the immune system alterations that confer tissue damage in SLE.'

HDL May Predict Lupus Atherosclerosis

BY NANCY WALSH
New York Bureau

BIRMINGHAM, ENGLAND — Patients with lupus who have high levels of proinflammatory high-density lipoprotein may be at particular risk for atherosclerosis and therefore could be suitable candidates for prophylactic treatment, Bevra Hahn, M.D., said at a joint meeting of the British Society for Rheumatology and the German Society for Rheumatology.

Recognition of the prevalence and lethality of atherosclerosis in systemic lupus erythematosus (SLE) has led to increased interest in strategies to prevent its onset and progression, such as with statin therapy.

"We know that 30%-40% of lupus patients have carotid plaque, coronary artery calcifications, or some other manifestation of atherosclerosis, but we found that only 15% of patients in our cohort had any lipid abnormalities, so it didn't seem very reasonable to just put them all on statins," said Dr. Hahn, professor of medicine and chief of rheumatology, at the University of California, Los Angeles.

Caution also is needed because the statin drugs have been reported to induce lupus-like syndromes with the development of antinuclear antibodies in an increasing number of patients. Statins also might aggravate lupus itself, possibly through enhancing the shift from a Th1 to Th2 immune response, which heightens B cell reactivity and increases the production of pathogenic autoantibodies (*Lupus* 2005;14:192-6).

So Dr. Hahn and her colleagues began looking for a new biomarker that might provide a more targeted population for statin therapy. "We reasoned that people with a chronic inflammatory disease like lupus might have a lot of proinflammatory HDL. That turned out to be right," Dr. Hahn said.

Proinflammatory HDL particles contain inadequate amounts of antioxidant enzymes such as paraoxonase. These components are replaced by serum amyloid and oxidation products, rendering the HDL particle incapable of its vital function of protecting LDL particles from becoming oxidized. Once oxidized, LDL contributes

to the early development of carotid plaque.

In a study at her center that included 153 patients with lupus, 45% were found to have proinflammatory HDL, as did 21% of a group of 44 patients with rheumatoid arthritis.

Fewer than 5% of a healthy control group had the abnormal HDL, Dr. Hahn said.

On multivariate analysis, the presence of proinflammatory HDL was highly correlated with increases in oxidized LDL, and was also correlated with coronary artery events, hypertension, and high erythrocyte sedimentation rate (ESR).

"So it looks like we might have one biomarker that would tell us which people are predisposed to atherosclerosis and should be treated for it," she said.

The next question is what that treatment should be. In patients who have had a myocardial infarction and have high levels of proinflammatory HDL, statins do lower the levels, but not even close to the normal range, Dr. Hahn said.

"My personal opinion is that statins may be helpful but, if we are right about what is important in lupus atherogenesis, they won't be enough. I think the most effective therapy will be one that actually suppresses SLE activity," she said. ■

'My personal opinion is that statins may be helpful but, if we are right about what is important in lupus atherogenesis, they won't be enough.'

Takayasu's Case Resolved With Infliximab Tx

BY NANCY WALSH
New York Bureau

BIRMINGHAM, ENGLAND — Tumor necrosis factor blockade may offer a successful therapeutic alternative to high-dose corticosteroids in the rare, potentially life-threatening occlusive vasculitis known as Takayasu's arteritis.

This large-vessel vasculitis typically involves the aorta and its main branches, causing stenosis or even obstruction. It occurs most commonly in young women.

In a case report presented at the joint meeting of the British Society for Rheumatology and the German Society for Rheumatology by Lucy E. Coates, M.D., of the Royal National Hospital for Rheumatic Diseases in Bath, England, a 17-year-old female patient developed severe left-sided facial pain that radiated into her neck and left arm.

Initially, the symptoms were thought to be musculoskeletal in origin, and she was treated with physiotherapy, analgesics, and tricyclic antidepressants.

Subsequent investigations, however, revealed the presence of markedly elevated inflammatory markers, including a plasma viscosity of 2.41 millipascal seconds (normal range 1.50-1.70 mPa·s).

She also had microcytic anemia, and levels of immunoglobulins were raised, with IgG at 17.4 g/L, IgA at 4.2 g/L, and IgM at 3.8 g/L. Various imaging studies were done, including MRI of the brain and cervical spine and CT of the abdomen and pelvis, without result.

Two years later, a lump was discovered in her neck. On examination, she was found to have bilateral carotid bruits. Magnetic resonance angiography (MRA) results showed thickening in the wall of the right brachiocephalic artery, narrowing the vessel. The subclavian artery was narrowed at its origin and underfilled distal to its origin. This was suggestive of a proximal stenosis such as is seen in Takayasu's arteritis, Dr. Coates said.

The patient was started on prednisone and azathioprine, but 1 year later her symptoms had worsened, as had the imaging findings on repeat MRA. The decision was made to institute more aggressive therapy because of concerns that the blood vessels supplying her brain were being affected, Dr. Coates said in a poster session.

Infliximab treatment was begun, with infusions of 5 mg/kg at weeks 0, 2, 6, and 10 and then every 6 weeks.

She also continued to take azathioprine (100 mg/day) and prednisone (20 mg/day). Symptomatic improvement was immediate, and another MRA the following year showed significant improvement in the caliber and appearance of the aortic arch vessels.

"Anti-TNF therapy appears to offer a promising alternative in Takayasu's arteritis, particularly if other forms of immunosuppression fail to control progression," Dr. Coates said in her poster presentation.

Her findings support those seen in another recent series in which 14 of 15 patients with the condition responded and 10 experienced sustained remission and were able to discontinue glucocorticoid therapy (*Arthritis Rheum.* 2004;50:2296-304). ■