Urinary Biomarkers Detect SLE Nephritis Flare

BY NANCY WALSH
New York Bureau

NEW YORK — Monitoring the urinary excretion of monocyte chemoattractant protein-1 and adiponectin may prove to be a novel and specific means of evaluating renal activity and injury in patients with systemic lupus erythematosus, according to Dr. Brad H. Rovin.

There is substantial evidence suggesting that the proinflammatory chemokine monocyte chemoattractant protein-1 (MCP-1) is involved in the pathogenesis of renal injury in nephritis associated with systemic lupus erythematosus (SLE). "The main function of inflammatory chemokines is to regulate the deployment of leukocytes to tissue sites undergoing pathological change. These chemokines also activate leukocytes and may promote tissue fibrosis," Dr. Rovin said at a rheumatology meeting sponsored by New York University.

The relationship of MCP-1 with lupus nephritis has now been investigated in patients enrolled during the past 5 years in the longitudinal Ohio SLE Study. The cohort includes 71 patients with lupus nephritis and 35 patients with SLE but with no evidence of renal involvement.

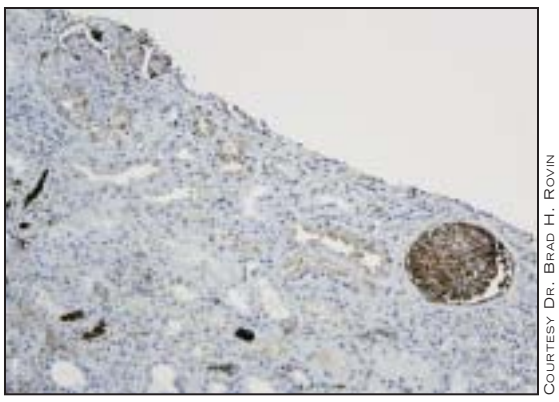
With a mean follow-up time of approximately 32 months, there have been 70 renal flares and 88 nonrenal flares in the patients.

Urinalysis performed every 2 months found that the mean level of MCP-1 of patients at renal flare was significantly higher than that of any of controls, with 73% of flare values being above the 95th percentile of those of disease control patients (J. Am. Soc. Nephrol. 2005;16:467-73). Patients with class IV glomerulonephritis, with crescents and necrosis, had the highest levels of MCP-1, which reached 12,000 pg/mg creatinine.

High levels of MCP-1 during flare also were associated with manifestations of renal injury including changes in serum creatinine levels and proteinuria.

Among patients with impaired renal function whose serum creatinine was elevated at 1.2-5.5 mg/dL, the mean MCP-1 was significantly higher, at 2,719 pg/mg creatinine, than in those with normal renal function, who had a mean level of 846 pg/mg creatinine.

At the time of flare, most patients had been receiving immunosuppressive therapy with prednisone and agents such as mycophenolate mofetil, and even such substantial therapy was inadequate to suppress MCP-1. "This shows that the current therapies we have to treat lupus nephritis do not adequately suppress the expression of this particular chemokine," said Dr. Rovin, professor and director of the division of nephrology, Ohio State University, Columbus.



COURTESY DR. BRAD H. ROVIN

Staining for adiponectin in a kidney biopsy from a patient with class IV SLE nephritis shows injury.

Response to increased immunosuppressive treatment following flare also correlated with MCP-1. In the majority of patients, MCP-1 decreased with treatment, although only gradually, but in a subset, MCP-1 remained persistently elevated. "We wonder if this is a biomarker for ongoing inflammatory injury in the kidney, and if these patients might benefit from prolonged therapy. We don't know the answer to that," he said.

These findings suggest that monitoring this cytokine might be a novel way of monitoring disease activity and response to treatment, he said. And because MCP-1 appears not to be simply a biomarker but actually is involved in organ injury, therapies directed at the cytokine itself may be beneficial and are being investigated.

A proteomic approach also has identified the adipocyte-derived cytokine adiponectin as another "totally unexpected" marker of lupus nephritis, he said.

Adiponectin, which is also produced by other cells such as fibroblasts and synovial cells during periods of inflammation, originally was studied in metabolic disorders and was found to enhance insulin sensitivity and to be underexpressed in obesity and diabetes.

It has now been shown to modulate inflammation, with both anti-inflammatory and proinflammatory effects. Its proinflammatory effects include the activation of the transcription factor NF-ℜ B (NF-KB) and increasing the production of MCP-1 and interleukin-8 by endothelial cells and blood monocytes (Clin. Immunol. 2006;120:99-105).

Recent work has found that both adiponectin and its receptor are expressed in the kidney, suggesting the possibility that this cytokine also has a direct, but as yet unspecified, effect on renal cell function, Dr. Rovin said.

As is the case with MCP-1, levels of adiponectin in the urine are increased during renal flare but not during nonrenal flare, correlating with plasma levels and magnitude of proteinuria (Kidney Int. 2005;64:1825-33). ■

Treatment May Hurt, Not Help, Most Pulmonary Sarcoidosis

BY SHARON WORCESTER
Southeast Bureau

DESTIN, FLA. — Treatment is not necessary in all patients with pulmonary sarcoidosis, Dr. Marc Judson said at the annual Rheumatology on the Beach.

More than two-thirds of patients with this form of sarcoidosis, which accounts for the vast majority of cases, will spontaneously remit. Thus the side effects of corticosteroids, the most common form of treatment, often are not worth the limited benefits, said Dr. Judson, professor of medicine at the Medical University of South Carolina, Charleston.

Furthermore, some retrospective evidence suggests corticosteroid treatment promotes relapse. In one study, more than 70% of treated patients relapsed, versus less than 10% who received no treatment, according to Dr. Judson. In another, the relapse rate was higher in patients who received a mean dose of 17 mg of prednisone daily, versus a mean dose of 10 mg daily.

He recommends using a decision analysis based on prognostic factors and degree of pulmonary function in patients with pulmonary sarcoidosis, whereby asymptomatic patients are untreated, and those with mild pulmonary dysfunction and minimal functional limitation are observed without treatment. These patients are likely to experience spontaneous remission.

Patients with an excellent prognosis (see sidebar) are also observed, but palliative care can be attempted when necessary—such as in those who develop severe sarcoid arthritis. Nonsteroidal anti-inflammatory drugs can help in these patients, he said.

In those with mild to moderate pulmonary dysfunction and mild to moderate functional limitation, treatment and observation for deterioration are both acceptable, but Dr. Judson recommends observation initially, with treatment for deterioration, and a steroid trial if no improvement is seen within 3- 6 months.

Prednisone at 20-40 mg per day for 2-6 weeks is recommended in those who do undergo treatment. After the initial 2 to 6-week dosing regimen, the dose is tapered over 1-3 months to a maintenance dose, which is used for 3-9 months. The patient is then tapered off the drug over 1-3 months, followed by an observation period and a second trial in those who relapse.

Other treatment options include methotrexate, pentoxifylline, chloroquine, azathioprine, and infliximab. Methotrexate is the most studied and appears to have some benefit; azathioprine appears to have the least, he said.

Recent data on infliximab are promising. Dr. Judson and his colleagues found the overall change from baseline was 2.5% predicted forced vital capacity at 24 weeks in 93 patients treated with either 3 or 5 mg/kg of infliximab. The change was statistically significant. Furthermore, some patients had only mild disease; patients were also treated with prednisone; and the 2.5% change from baseline was in addition to benefits seen with prednisone.

Dr. Judson received research grants from Centocor, maker of infliximab. ■

When to Treat Pulmonary Sarcoidosis With Corticosteroids

Disease Severity	Treatment
Asymptomatic patient	No treatment
Mild pulmonary dysfunction/minimal functional limitation	Observation/no treatment
Patients with excellent prognosis (such as those with erythema nodosum, early-stage disease)	Observation/palliative treatment as warranted
Mild to moderate pulmonary dysfunction or functional limitation	Treatment or observation for deterioration. Treat in the event of deterioration or if no improvement is seen in 3-6 months.
Severe pulmonary dysfunction or functional limitation	Treat

Source: Dr. Judson

ELSEVIER GLOBAL MEDICAL NEWS

Factors Can Predict Sarcoidosis Outcomes

Data suggest most patients with sarcoidosis will have spontaneous remission with or without treatment, while up to a third will develop chronic disease.

A literature review suggests there are several factors that can predict a good (likelihood of remission) or poor (likelihood of chronic disease development) prognosis.

Stage I vs. stage II-III disease as determined by chest x-ray and the presence of erythema nodosum appears to be linked to a good prognosis, Dr. Judson said.

The following predict poor prognosis: black race, extrathoracic disease, age 40 years or more, splenic involvement, lupus pernio, disease duration over 3 years, forced vital capacity less than 1.5 L, and stage IV disease/aspergilloma on chest x-ray. The latter two factors are also risk factors for death from sarcoidosis.

However, death from the disease occurs rarely (in 3%-5% of patients).