Averting Renal Crisis in Scleroderma Has Dark Side

BY NANCY WALSH
New York Bureau

NEW YORK — The marked decrease in mortality relating to renal crisis in patients with scleroderma because of the widespread use of ACE inhibitors has been accompanied by a huge increase in deaths from lung disease.

"Current treatment of scleroderma lags far behind some of the great successes we have seen in other rheumatic diseases. It has the highest mortality, with a 10-year survival of only 55%," Dr. John Varga said at a rheumatology meeting sponsored by New York University.

Immunosuppressive therapies have been largely ineffective in scleroderma. "Steroids don't work and are probably contraindicated, and experience with methotrexate and the tumor necrosis factor inhibitors has not been very positive," he said.

However, "we have learned a great deal about what happens with scleroderma vasculopathy," said Dr. Varga, professor of medicine at Northwestern University, Chicago.

The most important vasculopathy in scleroderma is pulmonary arterial hypertension (PAH), Dr. Varga said. "This has always been the case, but until 2 decades ago we didn't even know how to recognize it, and because there was essentially no treatment, there was very little interest in trying to study it," he said.

PAH develops in approximately 10%-20% of patients with scleroderma, and often manifests late in the disease. "Survival is abysmal," he said, and although newer treatments currently in use may change this, the survival data are not yet available. In any case, because PAH is such a serious and prevalent complication, it is important for clinical rheumatologists to screen for it and to do so early, he said.

The most common screening study is Doppler echocardiography, which is easily reproducible, noninvasive, and relatively inexpensive. However, this test has many false positives and false negatives and cannot differentiate PAH from pulmonary vascular hypertension, for which the treatment is very different. Right heart catheterization is needed for anyone with suspected PAH or rapidly falling diffusing capacity, according to Dr. Varga.

Better understanding of the key signaling pathways in PAH, such as the endothelin pathway, has led to the development and approval of agents such as bosentan, sildenafil, and ambrisentan. Currently there is considerable interest in combination therapy and goal-directed therapy, in which specific target goals and time frames are set and, if not met, the drug dosages are increased.

Good evidence from the Scleroderma Lung Study shows Cytoxan slows interstitial lung disease.

DR. VARGA

There also is good evidence now that cyclophosphamide (Cytoxan) slows interstitial lung disease, as was shown in the Scleroderma Lung Study. In that trial, 158 patients with alveolitis were randomized to cyclophosphamide or placebo and followed for 12 months. Those on standard therapy showed marked decline in lung function, while disease stabilized among those on the active treatment (Arthritis Rheum. 2007;56:1676-84).

Small but significant benefits were seen on skin scores, and some improvements were reported on the health assessment questionnaire as well as on the symptom of breathlessness—which was very important for the patients, said Dr. Varga, who participated in the trial.

"These results were encouraging, although there was debate as to whether the risk of Cytoxan was worth these fairly modest benefits," he said.

Further follow-up found that benefits of cyclophosphamide on forced vital capacity continued through 18 months, but thereafter began to wane and was lost at two years. "Perhaps these patients should have a second treatment," he suggested.

Targeting the pathways and mediators involved in fibrosis is another new and exciting area of research and clinical development, Dr. Varga said.

One profibrotic mediator of interest is transforming growth factor β (TGF-β), which is a ubiquitous growth factor with pleiotropic effects that act through the Smad pathway.

Small molecules have been developed that specifically block this pathway; in animal models they look promising, but no clinical data are yet available. ■

Preemptive Corticosteroids Prevent Serious Lupus Flares in Stable Patients

BY NANCY WALSH
New York Bureau

NEW YORK — Short-term moderate-dose corticosteroids might avert serious flares in clinically stable lupus patients who show elevations of certain serologic disease markers, Dr. H. Michael Belmont said at a rheumatology meeting sponsored by New York University.

"Our hypothesis was that if we had a sufficiently reliable biomarker, we could predict in a reasonable way a lupus flare and intervene with an appropriate anti-inflammatory," said Dr. Belmont, director of the lupus clinic at Bellevue Hospital and with the department of medicine, New York University, New York.

Analysis of pooled samples from 496 women enrolled in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial showed increases in anti-double-stranded DNA (anti–dsDNA) antibodies and the complement degradation product C3a predicted severe disease flare in patients with clinically quiescent disease, he said.

Based on this finding, a prospective trial was undertaken to determine whether preemptive therapy could avert severe flares and the damage that can result.

A total of 180 patients with stable disease were enrolled. Patients were eligible if anti-dsDNA antibodies had been present within the past 2 years, they required daily prednisone doses below 15 mg, had no active infection, and had been on a stable drug regimen for 2 months.

They were evaluated monthly for 12-18 months with measurements of various analytes including C3, C4, CH50, C3a, and anti-dsDNA. Clinical status was assessed according to the SELENA version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and physician global assessment.

At any point in the trial, clinically stable patients who had increases in anti-dsDNA antibodies of 25% or more and of C3a by 50% since the previous visit were randomized to placebo or an increase in prednisone to 30 mg/day for 2 weeks. The dose was then tapered to 20 mg/day for 1 week and to 10 mg/day for an additional week.

A total of 41 patients flared and were randomized, 21 to prednisone and 20 to placebo. There were no statistically significant differences between the two groups; 90% were female, mean age was 35 years, disease duration averaged 7 years, and mean SLEDAI was 4.2. Mild to moderate flares were seen in two patients receiving placebo and in four receiving prednisone within 90 days of randomization. "However, the major finding was that of 21 patients who received prednisone, none experienced a severe flare, while among the 20 who received placebo, 6 had severe flares, which was a highly significant difference," Dr. Belmont said.

Analysis revealed that at 1 month, there were three renal and one central nervous system flare, and at 2 months, one patient developed pyoderma gangrenosum and pancytopenia. At 3 months, there was an additional case of pleural effusion with fever and dyspnea.

Prednisone also led to significant benefits on SLEDAI, anti-dsDNA, C4, and C3a after 1 month.

"What price did patients pay for receiving the preemptive prednisone? It turned out that there was a slightly greater absolute number of adverse events in the placebo group, at 13, compared with 10 events in the prednisone group," he said. So the short-term increase in prednisone did not result in an increased risk of adverse events, and despite the fact that patients randomized to prednisone initially had greater exposure to the drug, the cumulative exposure was greater in those who flared. Three patients who flared also required initiation or increase in cytotoxic therapy.

"Consideration should be given to preemptive use of short-term moderate-dose corticosteroids in clinically stable, serologically active lupus patients to prevent severe flares and prolonged exposure to high-dose corticosteroids and additional cytotoxic agents," he said. ■

Novel SLE Biomarkers May Help Rapidly Assess Activity

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — Promising new biomarkers of complement turnover may provide a rapid measure of lupus activity over a defined time period.

This would be enormously helpful to physicians in monitoring disease activity accurately, predicting flares, and adjusting treatment accordingly. Measurement of C3 and C4, long the standard means of assessing the disease state, leave much to be desired, Dr. John P. Atkinson observed at a symposium sponsored by the American College of Rheumatology.

The novel biomarkers are the result of pioneering work by Dr. Joseph M. Ahearn and his colleagues at the University of Pittsburgh. They took advantage of the fact that in times of increased systemic lupus erythematosus (SLE) activity patients experience accelerated complement turnover.

The investigators identified fragments of the cleaved complement and showed that these fragments are deposited on the surface of many types of cells, including RBCs, platelets, and polymorphonuclear neutrophils. The amount of deposited complement-activation product C4d correlates with disease activity, while complement receptor type 1 deposition varies inversely with SLE activity, explained Dr. Atkinson, the Samuel B. Grant Professor of Clinical Medicine at Washington University at St. Louis.

The half-lives of RBCs, platelets, and polymorphonuclear neutrophils are about 60 days, 7 days, and 3 days, respectively. Depending upon which cell type is assessed for fragment deposits, physicians can obtain a picture of SLE activity over the course of a very different period of time.

Also, there is some preliminary evidence to suggest platelet C4d deposition might predict future vascular events in SLE patients with antiphospholipid antibodies.

Clinical trials are underway to assess the clinical utility of the new biomarkers.

The rheumatologist disclosed he has no financial conflict of interest with regard to the biomarkers but serves as a consultant to or is on the scientific advisory boards of several pharmaceutical companies. ■