# Combined Biomarkers May Predict Lupus Flare

BY NANCY WALSH
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NEW YORK — Combined elevations in two traditional markers—the sensitive complement protein C3a and antibodies to double-stranded DNA—can be used to predict severe disease flares in systemic lupus erythematosus and to guide implementation of preemptive treatment, Dr. H. Michael Belmont said at a rheumatology meeting sponsored by New York University.

These markers are useful in the diagnosis of systemic lupus erythematosus (SLE), and are routinely used to track disease activity and predict flares, but whether serial measurements could be used to follow clinically quiescent disease and serve as a basis for therapeutic decision making has remained controversial.

In an earlier study, asymptomatic patients with rising titers of anti–double-stranded DNA (anti-dsDNA) who were treated with prednisone had fewer severe flares and required less immunosuppressive therapy, but the difference compared with placebo did not reach statistical significance (Lancet 1995;345:1595-9).

"We therefore embarked on the serologically active, clinically stable lupus trial, with the intent of evaluating the effect of short-term, moderate-dose corticosteroid treatment in preventing or averting flares when there was a simultaneous elevation of both plasma C3a and anti-dsDNA in patients whose disease was stable or inactive," said Dr. Belmont, director of the lupus clinic, at Bellevue Hospital and codirector of the lupus clinic at the Hospital for Joint Diseases, both in New York.

A total of 154 patients were enrolled into the 18-month observational phase of the trial. To be eligible, patients were required to have a history of anti-dsDNA positivity and to be receiving no more than 15 mg/day of prednisone. Inactive disease was defined as a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of 4 or less; and stable disease was defined as a SLEDAI of 5-12.

At monthly visits, levels of various complement proteins and anti-dsDNA antibodies were measured, and clinical disease activity was evaluated according to the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of SLEDAI and by physician's global assessment.

Serologic flare was defined as an elevation of anti-dsDNA antibodies of 25% or more, combined with an elevation in C3a levels by 50% to an absolute level of 500 ng/mL or more.

Patients who remained clinically stable but who experienced a serologic flare were then randomized to receive placebo or daily doses of 30 mg prednisone more than their baseline doses for 2 weeks. This was then tapered to 20 mg more than the baseline dose for another week and to 10 mg more than baseline for an additional week.

"The hypothesis was that we would find fewer severe flares with preemptive treatment with prednisone than with placebo," Dr. Belmont said.

A total of 41 patients were randomized, 20 to placebo and 21 to prednisone. Randomization was successful in that patients in the active treatment and placebo groups were comparable in all clinically important ways, he said.

The major finding of the study was that none of the patients in the prednisone group experienced severe flares, while six patients in the placebo group had severe flares, said Dr. Belmont. The benefit for having received steroids was statistically significant, he said.

Three of the severe flares involved nephritis, one was neuropsychiatric lupus, one involved pyoderma gangrenosum with pancytopenia, and one was fever and lupus pneumonitis.

Six patients, four of whom were in the prednisone group, had mild to moderate flares. Most of these were characterized by arthritis and required no additional treatment.

Benefits over and above preventing severe flare, including improvements in SLEDAI scores, also were seen in the prednisone group (Arthritis Rheum. 2006;54:3623-32). This study also questioned the price patients would pay in terms of adverse events for receiving the preemptive treatment of 30 mg prednisone more than baseline for 2 weeks.

"It was reassuring, in that side effects that could be associated with having increased steroids were no greater than in the placebo group," Dr. Belmont said.

The most common adverse events were upper respiratory tract infections, which were seen in three patients in the prednisone group and in six in the placebo group, and urinary tract infections, which were seen in three patients in the prednisone group and in two in the placebo group.

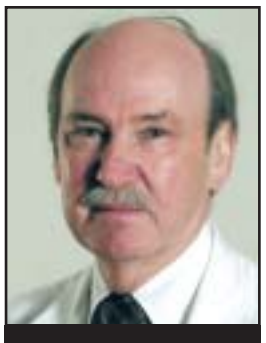
The preemptive treatment strategy using moderate-dose steroids did not result in an overall increased corticosteroid exposure in the treated group, compared with the placebo group, because the patients on placebo who experienced severe flares required high doses of prednisone. Two also needed the addition of cytotoxic agents. "This was important information," Dr. Belmont said.

"Using this study design as a guide, consideration should now be given to the preemptive use of short-term, moderate doses of corticosteroids in clinically stable, serologically active SLE patients to prevent severe flares and prolonged exposure to high-dose corticosteroids," he concluded. ■

## Ask the Expert

# Autoimmune Diseases: Could Stem Cells Be the Answer?

In the quest for new, viable treatment options for refractory autoimmune diseases, hematopoietic stem cell transplantation has emerged as a promising player. Traditionally considered a last-ditch strategy in the treatment of terminal hematologic illnesses, the infusion of healthy stem cells to replace the body's own malfunctioning ones following high-dose immunosuppression may restore immune function in individuals with severe autoimmune disease.



ALAN TYNDALL, M.D.

Several reports have documented cases in which stem cell transplantation to treat leukemia in patients with comorbid autoimmune diseases led to remission from both diseases. Additionally, in a report published last year, allogeneic hematopoietic stem-cell transplantation (HSCT) was associated with long-term remission of rheumatoid arthritis in two women who had undergone the procedure decades earlier as a treatment for drug-induced aplastic anemia (J. Rheumatol. 2006;33:812-3). More recently, a prospective trial of autologous hematopoietic stem cell transplantation (HSCT) in patients newly diagnosed with type 1 diabetes mellitus showed that the cellular therapy altered the disease course in 14 out of 15 of the patients treated, leading to sustained periods of insulin independence with only minimal treatment related toxicity (JAMA 2007;297:1568-76).

While the findings are encouraging, stem cell transplantation for the treatment of severe autoimmune disease is still experimental, according to Dr. Alan Tyndall, a rheumatologist at the University of Basel in Switzerland. "The experience worldwide has produced data on approximately 900 patients—850 for autologous HSCT vs. 50 allogeneic—with varying results. In both autologous and allogeneic, no response, long-term remissions, and relapses have been seen." Pivotal clinical trials, which are underway in Europe and the United States, will establish the place HSCT has in the treatment of autoimmune diseases, he said.

In this month's column, Dr. Tyndall discusses the promise and potential of HSCT in the treatment of autoimmune disease and which patients might be most likely to benefit.

**Rheumatology News:** What is the presumed mechanism by which stem cell transplantation induces remission in certain autoimmune conditions?

**Dr. Tyndall:** The presumed mechanism of action is a resetting of autoimmune responses, perhaps giving the regulatory cells a second chance. This has been shown in studies of multiple sclerosis (and in Still's disease). Therefore, the idea of eradicating every last autoreactive lymphocyte—similar to the concept of eliminating every malignant cell in other transplants—does not seem to be necessary.

**RN:** Are some autoimmune conditions more likely than others to respond to this type of treatment?

**Dr. Tyndall:** The more reversible inflammatory disease there is, the more likely an autoimmune disease will be to respond to an immunoablative therapy. So far, the most extensive data are from multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, and juvenile idiopathic arthritis, in which approximately one-third of the patients obtained durable remission.

**RN:** How important is the timing of treatment with respect to disease progression?

**Dr. Tyndall:** All of the data so far show that earlier is better than later. The stem cells do not repair tissue, as far as we know, they merely allow a large dose of immunosuppressive therapy to be given and to "rescue" the bone marrow afterward. The ideal patient is one who has early, inflammatory disease with a poor prognosis—that is, with no further conventional therapy options—but who is not so permanently damaged that an acceptable quality of life would not be possible after disease control. Also, the procedure should not be left until the patient is in a critically acute illness situation, because this makes the transplant procedure more dangerous.

**RN:** Is it likely that HSCT transplantation for autoimmune disease will move from research into practice any time soon?

**Dr. Tyndall:** Yes, at least for autologous HSCT, which is where most of our data come from. Before this happens, we have to finish the prospective randomized controlled trials that are currently underway, including the Autologous Stem Cell International Scleroderma (ASTIS) trial in Europe, which has randomized 90 patients so far out of a required 120 patients, and the Scleroderma Cyclophosphamide or Transplantation (SCOT) clinical trial being conducted in the United States under the auspices of the National Institutes of Health/National Institute of Allergies and Infectious Diseases. These are investigator driven, noncommercial trials, which makes them more difficult from a practical point of view. It is anticipated that they will be finished in about 2 years, so it is well within our sights. ■

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*By Diana Mahoney, New England Bureau*