

Persistent Proteinuria Predicts Renal Relapse in SLE

BY NANCY WALSH
New York Bureau

BARCELONA — Factors that were predictive of relapse in lupus nephritis after induction therapy were persistence of proteinuria and abnormal C4 levels, and patients having received cyclophosphamide for less than 2 years, Dr. Eva Salgado reported at the annual European Congress of Rheumatology.

Considerable variability is seen in the clinical course and response to therapy in patients with systemic lupus erythematosus (SLE) who develop nephritis, and it would be useful to identify factors that are associated with relapse so that more aggressive treatment could be used from the outset, explained Dr. Salgado of Hospital 12 de Octubre, Madrid.

A study was therefore conducted that included all 128 patients diagnosed with

SLE and nephritis in the rheumatology department of Dr. Salgado's hospital between 1977 and 2007.

A total of 114 of the patients were women, and more than 95% were white. Mean age at the appearance of nephritis was 30 years, and mean time from the diagnosis of SLE was 2 years.

Renal biopsy at the time of diagnosis of nephritis showed minimal changes in 2% of the patients, mesangial glomerulonephritis in 18%, focal proliferative glomerulonephritis in 12%, diffuse proliferative glomerulonephritis in 55%, and membranous glomerulonephritis in 13%.

At the time of initiation of induction

therapy, 29 patients had some degree of creatinine increase, Dr. Salgado wrote in a poster session.

Induction therapies included corticosteroids alone in 23% of patients, corticosteroids plus cyclophosphamide in 65%, azathioprine in 10%, and mycophenolate mofetil in 2%. Mean duration of induction therapy was 27 months.

A total of 71% of patients showed a complete response to induction therapy, while 24% had a partial response and 5% did not respond.

After the initial response, 59% received maintenance therapy with antimalarial drugs, azathioprine, or both.

During a mean of 13 years of follow-up,

34 patients experienced renal relapse, at a mean of 51 months after the end of induction therapy.

Multivariate analysis found that relapse was independently associated with persistence of abnormal C4 levels or residual proteinuria greater than 0.5 g/day after the completion of induction therapy, and duration of cyclophosphamide therapy for less than 2 years, according to Dr. Salgado.

Factors that were not predictive of relapse included histologic findings, age at SLE or nephritis diagnosis, delay in induction therapy, use of maintenance therapy, or other clinical characteristics.

Six patients developed end-stage renal failure and 14 died.

Relapse was predictive of long term renal failure but was not associated with increased mortality in this group of patients, Dr. Salgado observed. ■

Occurrence of renal relapse in patients with lupus nephritis was predictive of renal failure but was not associated with increased mortality.

Cyclophosphamide Is Safest When It's Infused

BY NANCY WALSH
New York Bureau

BARCELONA — Evidence from placebo-controlled trials now exists confirming that both oral and intravenous cyclophosphamide are beneficial in the treatment of scleroderma lung disease.

However, there are no head-to-head data identifying which route of administration is more effective or less toxic, so to address this question Dr. Daniel E. Furst reviewed the data for both in a presentation at the annual European Congress of Rheumatology.

Oral cyclophosphamide was evaluated in a double-blind study at 13 clinical centers throughout the United States. "We asked very simple questions: Would oral cyclophosphamide work in the lung and would it be worth the side effects of such a drug?" said Dr. Furst, who is Carl M. Pearson Professor in Rheumatology, University of California at Los Angeles, and who was one of the study investigators.

A total of 158 patients with diffuse or limited scleroderma were enrolled and randomized to receive oral cyclophosphamide, 2 mg/kg or less per day, or placebo for 1 year.

The primary end point was the percentage of predicted value of forced vital capacity (FVC) at 12 months.

At 1 year, the adjusted mean absolute difference in FVC between the cyclophosphamide and placebo groups was 2.53%, favoring cyclophosphamide (N. Engl. J. Med. 2006;354:2655-66).

The difference was significant but quite modest, the investigators pointed out. "These are very small changes, and all we can say about this outcome is that there is a statistical difference but not necessarily a clinical difference," Dr. Furst said.

Greater differences were seen on a secondary end point, the transitional dyspnea index. Scores improved by 1.4 points in the cyclophosphamide group and worsened by 1.5 points in the placebo group, which was quite significant and a

large enough difference to be clinically important, he said. Favorable effects also were seen on total lung capacity, functional ability, and Rodnan skin scores.

More adverse events were seen in the active treatment group, with leukopenia being the principal one. There were no statistical difference in numbers of serious adverse events between the two groups, and those that are attributable to cyclophosphamide also occurred in the placebo group, Dr. Furst said.

No information is available yet on possible long-term adverse events such as bladder cancer.

"We are following these patients but we have no answers yet," he said.

Intravenous cyclophosphamide was evaluated in the Fibrosing Alveolitis in Scleroderma trial (FAST), which included 45 patients from five centers in the United Kingdom. They were randomized to receive low-dose prednisone plus placebo or cyclophosphamide, approximately 1,000 mg/month for 6 months, and then oral azathioprine in doses of 2.5 mg/kg per day as maintenance therapy.

The FVC decreased about 5% in the placebo group and was stable in the cyclophosphamide group. The difference in change in FVC between the groups trended toward, but did not achieve, statistical significance (Arthritis Rheum. 2006;54:3962-70).

However, only about 60% of patients completed the trial. "And with such small numbers, it would have been a great surprise to see statistical differences," Dr. Furst said.

"In this case, you have to think differently—if it comes close that's very encouraging," he said.

The FAST investigators wrote, "We would suggest that a trend for improvement, intuitively better than a trend for decline, is hugely encouraging for the patient, and this must not be ignored."

They also noted that many patients with severe or deteriorating disease were excluded from the trial and that the small

therapeutic effects they saw in patients with milder disease might be greater in more progressive disease.

Adverse events associated with the active treatment were few, resulting in withdrawal in only two cases. There were no cases of hemorrhagic cystitis or bone marrow suppression.

"So you can see that both drugs work, but data from lupus and Wegener's trials tell us that, in general, if the intravenous administration is handled carefully, it is a little safer than the oral drug. So, for my patients, if they can tolerate the intravenous drug, I tend to go with that," Dr. Furst said.

It's important to provide clear instructions about increased fluid intake, to be cognizant of the potential for cardiovascular toxicity, and not to treat for too long, he said.

With regard to the duration of treatment, Dr. Furst said in response to a question from the audience that he tends to treat for about 6 months to 1 year and then give the patient a rest period for about 6-8 months.

"But in real life, sometimes patients only begin to respond at 3-6 months, and you might be reluctant to stop. If you go longer than a year, you have to discuss it with the patient, because of the possibility that 5 years down the road they may have a serious problem," he said.

Dr. Douglas J. Veale of University College Dublin, who was involved in FAST, offered a closing comment.

"I think you would agree that if we thought 10 years ago that we would be sitting in a room this big talking to this many people about any drug trial in systemic sclerosis, we would have been very excited. I think to have two trials showing benefits for patients is a remarkable achievement. The greatest need now is close collaboration from both sides of the Atlantic in designing similar studies with sufficient power," he said.

"I could not possibly agree more," Dr. Furst replied. ■

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Rx Drugs Disposal Guide Issued

New guidelines on the proper disposal of unused, unneeded, or expired prescription drugs were released by the White House Office of National Drug Control Policy, the Department of Health and Human Services, and the Environmental Protection Agency. To read the full guidelines, visit www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf.

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