Cytoxan Offers Modest Sclerosis Lung Benefits

The first RCT assessing the drug for interstitial lung disease showed a slowing in functional decline.

BY COLIN NELSON
Contributing Writer

The immunosuppressant drug cyclophosphamide may attenuate the decline in lung function that comes with scleroderma, according to a recent multicenter trial.

The investigation findings suggest that differences in lung function as small as 2%-3% may brighten the quality of life among scleroderma patients.

Loss of vital capacity in scleroderma "shortens life and increases morbidity," coauthor of the trial, Philip Clements, M.D., of the University of California, Los Angeles, said in an interview. Although lung function did not improve in patients taking cyclophosphamide (Cytoxan) in the trial, it deteriorated less than in those who took placebo, he said.

Some 60%-70% of patients with scleroderma die within 10 years. Most develop interstitial lung disease (ILD). Some 15% of patients will go on to severe lung disease with forced vital capacity (FVC) of less than 50% of normal.

The new trial, known as the Scleroderma Lung Study, is the first large, randomized, controlled, double-blind trial to investigate the influence of cyclophosphamide on lung function in scleroderma patients with ILD. The goal is to see whether cyclophosphamide is effective early in the course of ILD, before the disease does irreversible damage.

Dr. Clements and his colleagues enrolled 156 patients with scleroderma of less than 7 years' duration, who had shortness of breath, the appearance of "ground glass" on lung CT scans, and FVC less than 85% of predicted normal.

The researchers randomized patients to receive either cyclophosphamide or placebo (1 mg/kg per day initially, followed by increases of 25 mg every 4 weeks until the daily dose reached 2 mg/kg per day or was limited by toxicity). On average, the subjects were 48 years old and had had scleroderma for 3 years; 71% were female. Their FVC was 68%, total lung capacity was 70%, and diffusing capacity was 47%.

Of the 80 patients in the cyclophosphamide group, 72 were available for FVC measurements at either 9 or 12 months, as were 70 of 76 patients in the placebo group.

The authors recently presented the 12-month results of their 2-year study during a symposium at the 2005 annual meeting of the American Thoracic Society in San Diego

The results suggest that cyclophosphamide is modestly effective. Decline in FVC was 2.3% better in the cyclophosphamide group than in the placebo group.

The difference in lung function between groups is statistically significant, said Dr. Clements. "But whether it is clinically significant could be argued," he acknowledged.

Dr. Clements pointed out that cyclophosphamide might not help patients with long-standing, chronic disease. "The caveat here is that we looked only at early disease." Fibrosis in later disease may be more intractable, he suggested.

Results of the study's secondary outcomes were encouraging. Patients taking cyclophosphamide scored significantly better on the Transition Dyspnea Index, a measure of changes in breathlessness over time.

"It's pretty clear that the people who got Cytoxan had less shortness of breath," said Dr. Clements. "The people who took placebo got worse. It was a very strong effect." Skin thickening scores also improved significantly more in patients with diffuse scleroderma who received cyclophosphamide.

Cyclophosphamide appeared to provide significant improvements in subtle, subjective measures of self-rated health—in vitality and peppiness (as scored by the SF-36 scale) as well in health over time. Changes in the Health Assessment Questionnaire disability index scores were significantly better in the cyclophosphamide group at the 12-month mark, although these were considered "minimally clinically significant."

Less noxious drugs would clearly be helpful. Cyclophosphamide is 'a sledge hammer. Whether it is the right drug, we're still not sure.'

The news was not all good, however.

Dropouts in both groups were substantial. In the cyclophosphamide group, 26 of 80 patients (33%) stopped taking the drug by 12 months, according to Dr. Clements. In the control group, 21 of 76 patients (28%) stopped taking placebo.

Two side effects—a decreased white blood cell count and blood in the urine—were significantly higher in the cyclophosphamide group (at 19% and 11%) than in the placebo group (0% and 4%).

Patients taking cyclophosphamide had a higher number of serious adverse events (17 vs. 11), but the difference was not statistically significant. There was also no significant difference in the number of patients who developed pneumonia (five vs. one).

The authors attributed many of the adverse events to the natural course of the illness. "Scleroderma is a nasty disease," said Dr. Clements.

"You have not only potential lung disease, but also gut disease, heart disease, and kidney disease that are part of the scleroderma disease." With the exception of low white blood cell counts, he said, "The events are not necessarily related to the drug but to the disease."

Dr. Clements pointed out that some observers believe cyclophosphamide might be more effective than this trial suggests. Many patients with severe disease would simply not enroll in a placebo-controlled trial.

The decline in lung function among untreated patients with severe disease might have been greater than was seen in this trial, and thus would lead to a more pronounced difference between groups, these observers argue.

The best therapy for lung disease in scleroderma remains unknown.

According to Dr. Clements, preliminary results of a trial in the United Kingdom by Athol Wells, M.D., of Royal Brompton Hospital, London, and colleagues show dramatic improvements in lung function among patients receiving intravenous cyclophosphamide for 6 months—a 3% boost, compared with a 3% decline among those receiving placebo. After 6 months, the patients in the U.K. trial are switched to Imuran (azathioprine), a lesser immunosuppressive.

"In that context we have a confirmation that Cytoxan works and that immunosuppression helps," said Dr. Clements. Nevertheless, he added, less noxious drugs would clearly be preferable.

Cyclophosphamide is "a sledge hammer," he said. "Whether it is the right drug, we're still not sure." ■

Bosentan Yields Long-Term Improvement of Skin Scleroderma

BY NANCY WALSH
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VIENNA — The endothelin receptor antagonist bosentan, currently used for the treatment of pulmonary hypertension, also is showing long-term beneficial effects on digital ulceration and cutaneous fibrosis in patients with scleroderma.

Short-term improvements on digital ulcers associated with Raynaud's phenomenon in patients with systemic sclerosis have previously been reported, but a group of eight patients with ulcers that have not responded to other treatments—including intravenous iloprost—now have been treated with oral bosentan for up to 18 months with continued success, according to Juan J. Alegre-Sancho, M.D., and his colleagues in the department of rheumatology, Hospital Universitario Dr. Peset, Valencia, Spain.

Five of the patients in the study have diffuse cutaneous sclerosis, and three have a more limited form of the disease. All are women, with a mean age of 41 years and mean disease duration of 14 years.

At baseline, all patients had esophageal involvement, 63% had pulmonary fibrosis, 14% had pulmonary hypertension, 25% had cardiac involvement, and 63% had calcinosis and acro-osteolysis. Mean Rodnan skin score, which assesses skin thickening on a scale of 0 to 3 by clinical palpation at 17 body sites, was 21.

Previous treatments included calcium channel blockers, topical nitrates, losartan, aspirin, corticosteroids, and *D*-penicillamine. Hospitalizations for iloprost infusions had been required for four of the patients, Dr. Alegre-Sancho wrote in a poster at the meeting, which was sponsored by the European League Against Rheumatism.

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Ischemic digital ulcers present at baseline have healed in all patients, and the number, frequency, and time to healing of new ulcers have diminished in 63% of patients. In three patients who have been followed for 18 months and in five patients followed for 12 months, no new ulcers have developed.

The drug was given in standard dosages and was monitored according to recommended guidelines. The usual dosage of bosentan (Tracleer) is 125 mg twice daily, and patients must be followed for elevations in liver enzymes and for pregnancy prevention.

Raynaud's phenomenon has improved in frequency and severity of episodes in all patients, and three patients have been able to stop vasodilators.

Adverse events have generally been mild and transient, occurring in the first month of therapy.

In two patients, slight elevations of liver enzymes were seen, but these resolved spontaneously without dosage adjustment.

Bosentan treatment also has led to improvements in skin fibrosis, Dr. Alegre-Sancho noted in another poster session.

In these eight patients who were given the drug for ischemic digital ulcers and in three others who were being treated for scleroderma-related pulmonary hypertension, changes in skin thickness were seen beginning in the first month of therapy and continuing up to 18 months.

The improvements are first seen on the face, neck, chest, abdomen, and back; then gradually progress distally to the upper arms, thighs, forearms, and legs; and finally extend to the hands and feet.

All patients have recovered normal pigmentation, and the appearance of hyperhidrosis and hypertrichosis on the legs and arms of approximately one-third of patients suggests a recovery of normal skin structures, according to Dr. Alegre-Sancho. ■

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