

# Sildenafil Resolves PAH, Don't Use It Off Label

BY DOUG BRUNK  
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SEATTLE — A 12-week course of sildenafil citrate in adults with pulmonary arterial hypertension significantly improved 6-minute walking distance and mean pulmonary artery pressure, and had favorable effects on New York Heart Association functional class, H. Ardeschir Ghofrani, M.D., reported at the annual meeting of the American College of Chest Physicians.

"Sildenafil was not only highly effective in achieving improvement in 6-minute walking distance, but it also showed a very favorable safety profile," he said in an interview.

It appears to be a very "good drug" for treating pulmonary arterial hypertension, but as promising as these data appear,

physicians should not use the drug off label, as "this really should be addressed in controlled trials," Dr. Ghofrani said.

In a multicenter, international trial, Dr. Ghofrani and his associates enrolled 278 patients with pulmonary hypertension and randomized them to placebo or sildenafil three times daily for 12 weeks.

Most of the patients (75%) were female, and the average age was 49. Overall, 63% had primary pulmonary hypertension and 30% had connective tissue disease. Most of the patients (58%) had New York Heart Association functional class III disease and 39% had class II disease.

Of the 278 patients, 70 took placebo t.i.d., 69 took 20 mg sildenafil t.i.d., 68 took 40 mg sildenafil t.i.d., and 71 took 80 mg sildenafil t.i.d.

The primary end point was change

from baseline at week 12 in exercise capacity as measured by 6-minute walking distance.

Compared with patients who took a placebo, those assigned to take sildenafil had significant improvements in 6-minute walking distance.

The mean placebo-corrected treatment effect was 45 meters in the 20-mg group, 46 meters in the 40-mg group, and 50 meters in the 80-mg group.

"The improvements were slightly more pronounced in patients who had lower 6-minute walking distances at baseline, showing improvements up to 80 meters in the 80-mg group, whereas the patients who were doing better at baseline still had significant improvements," said Dr. Ghofrani of Giessen, Germany, who is a paid consultant to Pfizer, which manufactures sildenafil.

All sildenafil doses reduced mean pulmonary artery pressure by week 12. The mean reductions were 2.7 mm Hg in the 20-mg group, 3.0 mm Hg in the 40-mg group, and 5.1 mm Hg in the 80-mg group.

The proportion of patients who improved by at least one New York Heart Association functional class was 35% in the sildenafil group and 7% in the placebo group.

The investigators also observed a trend toward decreased hospitalizations and improvements in shortness of breath during exercise among patients on sildenafil.

The most common adverse events experienced by patients on sildenafil, compared with those on placebo, were headache, flushing, dyspepsia, and back pain.

Pfizer Global Research and Development funded the study. ■

## Screen Systemic Sclerosis Patients Early For Pulmonary Arterial Hypertension

BY MITCHEL L. ZOLER  
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MUNICH — Systematic screening of patients with systemic sclerosis for pulmonary arterial hypertension can identify patients with this life-threatening complication when it is less severe, based on a screening study with 617 patients.

Diagnosing pulmonary arterial hypertension (PAH) when it is not as advanced makes earlier treatment possible and may lead to better patient outcomes, Dr. Marc Humbert said at the annual congress of the European Society of Cardiology.

Systematic screening of 617 patients at 21 university hospitals in France identified 18 patients with newly diagnosed PAH. When added to the 29 patients from this group who had been previously diagnosed with PAH, there was an overall prevalence of PAH of 7.6% in patients with systemic sclerosis.

This was consistent with prior reports of a PAH prevalence of about 10% in these patients, said Dr. Humbert, a physician in the pulmonology service at Antoine Beclere Hospital, Clamart, France.

The 18 patients with newly diagnosed PAH had an average pulmonary artery pressure at rest of 30 mm Hg, compared with a mean, resting pulmonary artery pressure of 49 mm Hg in the 29 patients with previously diagnosed PAH.

The lower pulmonary artery pressure in the newly diagnosed patients showed that their disease was less advanced, Dr. Humbert said.

The 18 patients with newly-identified PAH had been diagnosed with systemic sclerosis for an average of 8 years.

By comparison, the 29 patients with established PAH had been diagnosed with systemic sclerosis for an average of 12 years.

When PAH develops in patients with systemic sclerosis, it usually appears 6-10 years after the disease manifests.

The screening study organized by Dr. Humbert and his associates enrolled patients who were at least 18 years old and had either diffuse or limited systemic scler-

rosis. During September 2002 through July 2003, there were 709 patients who met these criteria and were examined at the 21 participating centers.

The key screening measure was an echocardiography examination to assess the tricuspid-valve gradient. Patients who had a tricuspid regurgitation velocity of less than 2.5 m/sec were considered to have a low risk of having PAH and did not undergo additional testing, according to the study protocol.

Patients with a regurgitation velocity of more than 3.0 m/sec had a high risk of PAH and were referred for right heart catheterization.

Patients with a regurgitation velocity that fell within 2.5-3 m/sec were triaged to right heart catheterization if they also had a history of unexplained dyspnea. Patients in this range without a history of unexplained dyspnea did not undergo right heart catheterization.

A total of 92 patients were excluded from the study, mostly because of abnormal lung function or because they had received an incomplete echocardiography examination.

Among the 617 patients who remained in the investigation, 29 had known PAH and did not undergo further testing. Echo examinations of the other 583 patients yielded 51 patients with echo findings consistent with PAH.

Among these 51 patients, 33 agreed to have right heart catheterization, and 18 of these patients were found to have PAH.

An additional three patients were diagnosed with left heart disease.

Among the remaining 12 patients who underwent right heart catheterization, 6 had an elevated pulmonary artery pressure of more than 20 mm Hg, but this elevation failed to meet the minimum criteria for PAH of 25 mm Hg.

Among the 18 patients newly diagnosed with PAH, 14 had mild disease, with a resting pulmonary artery pressure of less than 35 mm Hg.

Another three patients had moderate PAH, with a resting pressure of 35-45 mm Hg, and one patient was diagnosed with severe PAH with a pressure greater than 45 mm Hg. ■

**Among the 18 patients newly diagnosed with PAH, 14 had mild disease, 3 patients had moderate disease, and 1 patient had severe pulmonary arterial hypertension.**

## Depression Common in Scleroderma Patients

SAN ANTONIO — The current and lifetime prevalence of major depression is high among patients with scleroderma, an underrecognized fact that can no longer be ignored, Thierry Baubet, M.D., said at the annual meeting of the American College of Rheumatology.

Among 94 patients with systemic sclerosis seen in two French medical centers between May 2002 and May 2004, 17 (18%) had a current diagnosis of major depression, 50 (53%) had a lifetime diagnosis of major depression, and 7 (7%) had a current diagnosis of dysthymia. Moreover, 12 had a history of suicide attempts, and 31 were judged to have a moderate to severe ongoing suicide risk, he said.

The patients ranged in age from 26 to 85 years, and 81 were women. Psychiatric assessment was done using the Mini-International Neuropsychiatric Interview, the French DSM-IV, the 13-item Beck depression inventory, and the hospital anxiety and depression scale.

Additional information regarding inpatient and current psychiatric treatment was sought with a structured questionnaire.

Fewer than half of patients with affective disorders had received psychiatric treatment, said Dr. Baubet of the psychiatric service, Avicenne Hospital, Bobigny (France).

Anxiety disorders also were common in this cohort, being diagnosed in 35 patients. Social phobia and generalized anxiety each were diagnosed in 13 patients, agoraphobia without panic disorder was diagnosed in 9, panic disorder in 6, posttraumatic stress disorder in 2, and obsessive compulsive disorder in 1. Some patients had more than one anxiety diagnosis.

Depression and anxiety are common and frequently overlooked in patients with systemic sclerosis, Dr. Baubet said in a poster session.

"Systematic screening and psychiatric treatment interventions are needed," he said.

—Nancy Walsh

