# Yearly PAH Screening in Scleroderma Is Crucial

BY MIRIAM E. TUCKER
*Senior Writer*

BALTIMORE — Scleroderma patients should have yearly screening for pulmonary arterial hypertension, Dr. Kwas Huston said at a conference on rheumatic diseases sponsored by Johns Hopkins University.

At Johns Hopkins' Scleroderma Center, all patients undergo annual screening for pulmonary arterial hypertension (PAH) with pulmonary function testing (PFT) and two-dimensional echocardiography. Asymptomatic patients with mild changes and right ventricular systolic pressure (RVSP) less than 40 mm Hg are rescreened at 6 months. Symptomatic patients with signs and/or abnormal two-dimensional echocardiography (RVSP greater than 40 mm Hg) undergo right heart catheterization to confirm the diagnosis.

"We now have treatments we didn't have 5 or 10 years ago. … The evaluation is important to identify pulmonary hypertension and for prognosis," said Dr. Huston, of the division of rheumatology at Johns Hopkins.

In the UNCOVER study published by Dr. Huston's group, 122 of 791 patients with scleroderma and mixed connective tissue disease seen in 50 community rheumatology practices had an existing diagnosis of PAH. But when the remaining 669 patients without a diagnosis of PAH subsequently underwent echocardiography, 89 had previously unrecognized PAH, for a total prevalence of 27% (Arthritis Rheum. 2005;52;2125-32).

Increased age at the onset of scleroderma is a major risk factor for PAH. Data from one study suggest that PAH risk increases 52% for every 10 years of age at disease onset, and that patients aged 60 and older have over twice the risk of younger patients (Chest 2003;124:2098-104). Other risk factors include severe Raynaud's phenomenon, low pulmonary diffusing capacity, calcinosis, Raynaud's disease, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome, he said.

PFT is useful for identifying PAH and for determining prognosis. In 71 scleroderma patients followed for a mean of 5 years, those with a carbon monoxide diffusing capacity (DLCO) of 40% or less had a 9% survival at 5 years, versus 75% among those with DLCO above 40% (Am. J. Med. 1984;77:1027-34). Pulmonary pressures were not measured in that study, but mortality is thought to be attributed to PAH, Dr. Huston noted.

The DLCO is also a useful predictor of who will develop PAH. In a retrospective case-control study of 212 scleroderma patients, the mean DLCO among the 106 with PAH was 52% of predicted 4.5 years prior to the PAH diagnosis, compared with 80% of predicted among the other 106 scleroderma patients who did not develop PAH (Arthritis Rheum. 2003;48:516-22).

Echocardiography is a useful companion screening tool. It had a sensitivity of 90% and specificity of 75% for identifying patients who had PAH on catheterization in a study of 33 scleroderma patients in whom clinical assessment, including ECG, chest x-ray, pulmonary function tests, and high-resolution computed tomography, raised suspicion of PAH (Br. J. Rheumatol. 1997;36:239-43). Echocardiography missed just two patients, both with pulmonary arterial systolic pressures (PASP) in the 30s. All patients with PASP above 40 mm Hg by echocardiography had abnormal pressures on catheterization.

As with PFT, echocardiography adds prognostic value. Increased mortality was tied to higher initial reading and with rising pressures in a study of 930 scleroderma patients, in whom mortality was 20% at 20 months among those with a single pressure of 30 mm Hg or greater. Rapid rises occurred more frequently in limited than in diffuse scleroderma (Rheumatology [Oxford]:2001;40:453-9).

In a study of 794 patients followed for 4 years, 3-year survival was inversely proportionate to mean PASP, from 75% among those with PASP under 32 mm Hg to 61% for 32-44 mm Hg, to 33% for pressures above 45 mm Hg (Ann. Rheum. Dis. 2003;62:1088-93).

Data support echocardiography and PFT for screening scleroderma, but Dr. Huston said areas of uncertainty include the role of exercise echocardiography in identifying patients with elevated right heart pressures on exercise but normal at rest, and the significance of a low-normal RVSP or low DLCO with normal echocardiography. ■

## Flawed Drugs Still Give Hope

While five of the approved medications for treating pulmonary arterial hypertension offer patients hope that was unavailable a few years ago, each has drawbacks, Dr. Huston cautioned. (For the newest approval, see story below.)

The five medications are three prostanoids (epoprostenol, treprostinil, and inhaled lipoprost), an endothelin antagonist (bosentan) and the phosphodiesterase inhibitor sildenafil. Each was approved by the Food and Drug Administration after short-term randomized controlled trials, usually lasting 12-16 weeks. "We don't know what to expect in the long term," Dr. Huston said.

The only drug to show a survival benefit was epoprostenol. Trials for the other drugs did not include enough patients to assess the drug's effect on mortality, and instead, used surrogate end points, like results of the 6-minute walk test or dyspnea questionnaires. Moreover, the large trials included patients with multiple causes of PAH, including scleroderma and lupus, groups that may not be comparable.

Epoprostenol requires a central intravenous line, the invasive nature of which carries an infection risk. The drug has a short half-life, which can lead to pump failure and disease worsening. Treprostinil can be infused subcutaneously and has a longer half-life, but a majority of patients experience pain at the infusion site. Inhaled lipoprost requires six to nine inhalations a day, and 10 minutes per inhalation, a process that patients find "a little cumbersome," Dr. Huston said.

Bosentan has the advantage of oral administration but is associated with abnormal elevations on liver function tests, and it interacts with several common drugs. It is contraindicated with cyclosporine and glyburide, for example. Sildenafil, called Revatio instead of Viagra when used to treat PAH, can potentiate hypotension when used with nitroglycerin. It also interacts with bosentan.

It is not clear which agent is best, or if combination therapy might help patients further, said Dr. Huston, who added he had no financial conflicts of interest to disclose.

# Sixth Drug for Pulmonary Artery Hypertension Gets FDA Nod

BY ELIZABETH MECHCATIE
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At least one shortcoming of currently available therapy for pulmonary arterial hypertension may become irrelevant with the Food and Drug Administration approval of the endothelin receptor antagonist ambrisentan last month.

In a statement issued by the FDA announcing the approval, Dr. John Jenkins, director of the FDA's Office of New Drugs, said that ambrisentan "is similar to an existing drug, but offers the potential for fewer drug interactions."

The FDA based its approval on findings from two studies of almost 400 patients that found treatment significantly increased physical activity capacity and delayed progression of the disease.

This is the sixth drug approved by the FDA for treating PAH; the others are epoprostenol, treprostinil, iloprost, bosentan, and sildenafil, which have all been approved over the last decade. Another endothelin receptor antagonist, sitaxsentan, is approved in Europe, Canada, and Australia, and has been under FDA review.

Over the last decade, the treatment options for PAH have expanded from a treatment that is administered in an intravenous infusion—epoprostenol—to treatments that include oral and inhaled medications, with wide use of combination therapy, because not all patients respond to monotherapy, said Dr. Lewis J. Rubin, professor of medicine at the University of California, San Diego.

The approved indication for ambrisentan is for treatment of PAH (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. Ambrisentan is being marketed under the trade name Letairis by Gilead Sciences Inc., which acquired Myogen Inc., the developer of the drug, in 2006.

The recommended dosage regimen is to start at 5 mg once a day, and if tolerated, to consider increasing the dosage to 10 mg once a day. Because it is teratogenic and has a potential risk of liver toxicity, the drug is available only through a restricted distribution program, the Letairis Education and Access Program (LEAP). Health care professionals, pharmacists, and patients must enroll in this program before they can prescribe, dispense, or receive the drug.

In an interview, Dr. Rubin said bosentan (Tracleer), the endothelin receptor antagonist approved for PAH in 2001, can interact with sildenafil, increasing the metabolism of sildenafil and reducing the metabolism of bosentan. (Sildenafil, marketed as Viagra for erectile dysfunction, is marketed as Revatio for PAH.) The two can be taken together, but optimal dosing is "challenging," he said.

Ambrisentan is taken once a day, compared with twice a day for bosentan, and the incidence of liver function abnormalities—the major potential toxicity of the endothelin receptor antagonist class—appears to be lower with ambrisentan based on available data, Dr. Rubin said. He added, however, that bosentan has been available longer, so there are more long-term data on the drug. Both appear to be equally efficacious, he said.

Dr. Rubin was the principal investigator of the ARIES-1 and ARIES-2 trials, which "demonstrated that ambrisentan is effective in a number of parameters of disease severity in patients with pulmonary hypertension and that it is a safe drug," he said. He also served as a consultant to Gilead in the development of the drug.

In the 12-week studies, 393 people with PAH received either placebo or ambrisentan added to current treatment (which could not include any of the drugs approved for PAH).

Compared with placebo, those on ambrisentan had significant improvements in the primary end point, the 6-minute walk distance, at 12 weeks. There was also a significant delay among those on ambrisentan in the time to clinical worsening of PAH.

The most common side effects associated with the drug were peripheral edema, a known class effect of endothelin receptor antagonists, which was usually mild to moderate; nasal congestion; sinusitis; and flushing, according to the FDA. The rate of treatment discontinuations because of side effects was similar (about 2%) for those on placebo and the drug.

Monthly liver function testing is necessary during treatment with ambrisentan. This is a pregnancy category X drug. ■

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