

Catheter Is Best for Diagnosing Scleroderma PAH

Echocardiograms aren't accurate enough, can't distinguish causes of pulmonary artery pressure.

BY M. ALEXANDER OTTO

EXPERT ANALYSIS FROM A RHEUMATOLOGY SEMINAR SPONSORED BY UCLA

MARINA DEL REY, CALIF. — Right ventricle catheterization is essential to confirm a diagnosis of pulmonary artery hypertension in patients with systemic sclerosis, according to Dr. Philip Clements, professor of medicine at the University of California, Los Angeles.

Doppler echocardiogram, which is the method used most often to diagnose pulmonary artery hypertension (PAH), is



Scleroderma can affect the upper lobes of the lungs, as seen above.

accurate to within 10 mm Hg only half the time, compared with catheterization.

More than a quarter of the time, it overestimates pulmonary artery pressure by at least 10-30 mm Hg, he said at a rheumatology seminar sponsored by the school. As a result, echocardiogram can lead to misdiagnosis and overtreatment, he said.

On top of that, it cannot distinguish between the causes of elevated pulmonary artery pressure.

In patients with systemic sclerosis, the cause of PAH is narrowed precapillary pulmonary arterioles.

In interstitial lung diseases, the cause is destruction of the pulmonary capillary bed, which elevates pressure.

And in left heart failure, a backup of blood in the pulmonary circulation elevates pressure, causing PAH, Dr. Clements said.

The different causes are treated differently.

"Can echo tell the difference?" Dr. Clements asked. "No. And before you put someone on \$100,000 of medications [for PAH], it would be nice to know that the patient actually has what you're about to treat," he said.

Right heart catheterization is moderately invasive, but in the hands of skilled cardiologists and pulmonologists, the

morbidity and mortality are low.

PAH is defined on catheterization as a mean pulmonary artery pressure greater than 25 mm Hg at rest, or 30 mm Hg during exercise.

The prevalence of PAH in scleroderma patients is about 16%-20%; women and older patients are those most affected.

PAH on exercise as well as a reduction in diffusion capacity of carbon monoxide are both early indicators that PAH at rest will eventually develop.

"Left alone, it is likely to progress," Dr. Clements said.

Whether PAH treatment makes a difference in the survival of scleroderma patients, however, is uncertain.

"The story so far is that the randomized controlled trials are short (3-4 months in duration) and done in small groups of patients. We want our patients to live for years. Unfortunately, we don't have years' worth of data," he said.

Despite those limits, Dr. Clements said the trial findings suggest that treatment can help, especially if it comes early and involves more than one agent.

In a randomized, placebo-controlled trial that included patients with connective tissue disease, 256 subjects with PAH on long-term background intravenous

epoprostenol were randomized to receive either sildenafil (20 mg t.i.d.) or placebo.

At the end of 16 weeks, the sildenafil group had a 28.8-m improvement in their 6-minute walk test distances, compared with the placebo group.

Sildenafil subjects also had greater drops in mean pulmonary arterial pressure, improvements in cardiac output, and longer time to clinical worsening. Quality of life improved as well (Ann. Intern. Med. 2008;149:521-30).

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Subgroup analyses of patients who were enrolled in randomized, controlled trials with bosentan, sitaxentan (not yet approved in the United States), and treprostinil have also shown favorable effects in scleroderma PAH patients, although with lower responses than in idiopathic PAH (Eur. Respir. J. 2009;34:1219-63).

Dr. Clements believes that combination therapy is likely to evolve for scleroderma PAH, just as it has for rheumatoid arthritis, hypertension, and a host of other medical problems.

Dr. Clements said the trial findings suggest that treatment can help, especially if it comes early and involves more than one agent.

Disclosures: Dr. Clements disclosed that he is a member of Gilead Sciences Inc.'s pulmonary hypertension advisory board.

Cyclophosphamide Is of Most Benefit for Worst SSc-ILD

BY M. ALEXANDER OTTO

EXPERT ANALYSIS FROM A RHEUMATOLOGY SEMINAR SPONSORED BY UCLA

MARINA DEL REY, CALIF. — Cyclophosphamide is most likely to help scleroderma interstitial lung disease patients early in the course of their disease if they have extensive lung fibrosis, high Rodnan skin scores, and documented declines in forced vital capacity, according to findings from an unpublished subgroup analysis presented by Dr. Philip Clements, professor of medicine at the University of California, Los Angeles.

The news comes from ongoing analysis of the Scleroderma Lung Study, and is soon to be published, according to Dr. Clements. He was a lead investigator in the randomized, controlled clinical trial, which compared a 12-month course of cyclophosphamide given to 79 patients with systemic sclerosis interstitial lung disease (SSc-ILD) against placebo given to 79.

At 18 months, treated patients improved slightly over baseline forced vital capacity (FVC), whereas patients in the placebo group declined. The treatment difference between the two groups was 4.16% in favor of the cyclophosphamide patients (Am. J. Respir. Crit. Care. Med. 2007;176:1026-34).

The treatment differences "collapsed at 24 months, unfortunately," Dr. Clements said.

However, in subsequent analysis, he and his col-

leagues identified a subset of patients who responded better to treatment: those with Rodnan skin thickness scores greater than 24 and fibrosis involving more than 50% of a lower-lung field.

Radiologists assessed the extent of lung fibrosis by visually inspecting high-resolution thoracic CT images. A software program has been developed to do the scoring, and should be available to clinicians within 3 years, Dr. Clements said.

For the subset of patients, FVC at 18 months in the treated group was 73% of predicted values for healthy, age-matched controls, but it was 63% of predicted values in the placebo group, although the treatment differences again collapsed at 24 months.

Even so, "the more fibrosis at baseline, the more likely [patients] are to respond," Dr. Clements said. "Thick skin suggests their lungs are likely to respond to cyclophosphamide." Additional analysis is planned to assess the clinical relevance of the findings, he said.

Patients from the Scleroderma Lung Study, which ran in 2000-2004, have been followed for an average of 8 years. So far, "cancer and death have not been associated with cyclophosphamide therapy," Dr. Clements said.

Given the results, he said he treats SSc-ILD patients with cyclophosphamide if they have mild to moderate restrictive lung disease and are within 7 years of scleroderma diagnosis.

They must also have FVCs that are lower than 80%

of predicted values, along with fibrosis involving 25% or more of any lung field accompanied by ground-glass opacifications and dyspnea involving difficulty in climbing two or three flights of stairs.

With those patients, "my treatment approach is similar to that of the National Institutes of Health's lupus nephritis protocol," Dr. Clements said. The protocol includes the following:

- ▶ Pulse cyclophosphamide IV (500-750 mg/m² per month (assuming normal renal function) for 6-12 months.
- ▶ Repeat pulmonary function tests every 3 months while patient is on cyclophosphamide.
- ▶ Upon completion of the infusion, switch to long-term mycophenolate mofetil (2-3 g/day orally).

Azathioprine (3-5 mg/kg per day) is an option if mycophenolate mofetil cannot be tolerated.

Mycophenolate mofetil is the subject of Scleroderma Lung Study II, which will compare a 2-year course of the drug in SSc-ILD patients against a 1-year course of cyclophosphamide, followed by placebo.

Mycophenolate mofetil "looks promising," Dr. Clements said, based on several small, observational studies.

About 30 patients have enrolled in the trial since last November. "We need 150," he said.

Information on the trial can be accessed on the Web at <http://sls.med.ucla.edu>. The trial is also listed on clinicaltrials.gov.

Disclosures: Dr. Clements disclosed that he is a member of Gilead Sciences Inc.'s pulmonary hypertension advisory board.

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