Bosentan Slows Progression in Class II PAH

BY MITCHEL L. ZOLER
Philadelphia Bureau

VIENNA — Patients with functional class II pulmonary arterial hypertension had significantly slower disease progression when treated with bosentan in a study with 185 patients, a finding that may shift the time to diagnose and start treatment of this disease.

The results support starting treatment of pulmonary arterial hypertension "as soon as possible after the diagnosis," Dr. Nazzareno Galiè said at the annual congress of the European Society of Cardiology. "In PAH it's very important to prevent deterioration, and that's what treatment with bosentan does. The results show that PAH is a progressive disease, even in class II, highlighting the need for early diagnosis and treatment."

The Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients (EARLY) study "is the only study to focus on class II patients," and it included a strict definition of class II, said Dr. Galiè, professor of cardiology and head of the Pulmonary Hypertension Centre at the University of Bologna, Italy.

Based on these and other findings, applications have been filed with the Food and Drug Administration and similar agencies in other countries to expand bosentan treatment to patients with class II PAH. Bosentan (Tracleer) is already marketed for treating classes III and IV PAH by Actelion. The new study was sponsored by Actelion, and Dr. Galiè is a speaker for and consultant to Actelion.

"The EARLY study results, and the results from [five] other studies that included class II PAH patients, support the benefit of treating patients with less-severe PAH. The added strength of the data from EARLY is that they demonstrated in a pure cohort of class II patients that early treatment may delay progression of the disease," commented Dr. Lewis J. Rubin, a coauthor of the study and professor of medicine and director of pulmonary and critical care medicine at the University of California, San Diego. Dr. Rubin is a consultant to Actelion.

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DR. RUBIN

The study enrolled patients aged 12 years and older, mean age 44, with PAH rated as functional class II by World Health Organization criteria. The disease could have been idiopathic (as it was in about 60% of patients), or caused by congenital heart disease (17%), connective tissue disease (18%), or HIV infection (5%). The average duration of PAH was about 3 years. Patients were randomized to treatment with either 62.5 mg bosentan b.i.d. for 4 weeks, followed by 125 mg b.i.d. for 5 months, or placebo.

After 6 months of therapy, pulmonary vascular resistance (one of two primary end points) rose from baseline by about 7% among 88 evaluable patients in the placebo group, and fell by about 16% in 80 patients in the bosentan group. The overall effect of bosentan therapy was to lower pulmonary vascular resistance by 23%, compared with placebo, a statistically significant effect.

The second primary end point was change in exercise capacity, measured by distance walked in 6 minutes. By this measure, bosentan was linked to a significant, 19-m boost in distance walked, compared with placebo, Dr. Galiè reported.

Bosentan treatment also led to significant improvements in time to clinical worsening, and a reduction in the percentage of patients whose condition worsened. Symptomatic progression of PAH occurred in 10% of patients on placebo, compared with 1% of the patients treated with bosentan. "With bosentan, there is more preservation of functional class," Dr. Galiè said. Bosentan also led to significant improvements in self-rated quality of life, and a significant reduction in serum levels of NT-probrain natriuretic peptide (NT-proBNP). The drug was well tolerated, with an adverse event profile similar to the placebo group.

To boost the number of patients with PAH who start treatment early, Dr. Galiè suggested screening for PAH in groups that are known to have a relatively high prevalence of PAH. This includes patients with connective tissue diseases, such as scleroderma, patients infected with HIV, and patients with congenital heart disease.

Three other reports at the meeting dealt with using bosentan to treat PAH; all three studies also were sponsored by Actelion.

One study showed that treatment with bosentan was safe and led to improvements in pulmonary vascular resistance and other measures, Dr. Irene Lang, professor of vascular biology at the Medical University of Vienna, reported at the meeting. Treatment also significantly boosted cardiac index, and cut NT-proBNP levels and dyspnea scores. Another study showed that a single dose of sildenafil in patients on chronic bosentan treatment was safe. The third study showed that the children's formulation had a good safety profile.

"New drugs such as bosentan have dramatically improved outcomes for patients with pulmonary arterial hypertension," said Dr. Daniel Jones, professor of medicine and dean of the medical school at the University of Mississippi, Jackson, and president of the American Heart Association. ■

Treatment of Pulmonary Arterial Hypertension Is Evolving

BY NANCY WALSH
New York Bureau

NEW YORK — As an increasing number of medical therapies become available for the treatment of pulmonary arterial hypertension and clinical experience accrues, questions have begun to arise as to how to initiate and optimize treatment, and how best to assess response, according to Dr. Harold I. Palevsky.

"There was a time when the treatment of pulmonary hypertension was very simple. All we had to decide was whether or not a patient was capable of managing intravenous prostacyclin," Dr. Palevsky said at a meeting sponsored by the Pulmonary Hypertension Association and the University of Michigan.

Now clinicians can choose from six Food and Drug Administration–approved therapies from three therapeutic classes, in addition to supportive therapies such as supplemental oxygen, digoxin, diuretics, and anticoagulants.

The three available prostacyclin derivatives are intravenous epoprostenol, inhaled iloprost, and subcutaneous or intravenous treprostinil. The two approved endothelin receptor antagonists are oral bosentan and oral ambrisentan, and the phosphodiesterase type 5 inhibitor is oral sildenafil.

Initial therapy is based primarily on an assessment of the patient's current and future risk, said Dr. Palevsky, professor of medicine, University of Pennsylvania, and director, pulmonary vascular disease program, University of Pennsylvania Health System, Philadelphia. A global risk assessment for the individual patient includes evaluation of WHO (World Health Organization) functional class, 6-minute walk test, serum B type natriuretic peptide (BNP) level, and echocardiography of right heart function. In addition, catheterization measures of pulmonary and cardiac pressures and cardiac output must be considered.

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DR. PALEVSKY

Accordingly, a patient with PAH and mildly impaired functional status, a 400-m 6-minute walk test, minimally elevated BNP, normal right heart function, and normal or near normal cardiac index would be considered low risk and a likely candidate for oral therapy, Dr. Palevsky said.

In contrast, the patient in WHO class IV, with a 6-minute walk test distance of less than 300 m, elevated BNP, and significant right ventricular dysfunction may require a more complex regimen involving inhaled or infused therapy.

Once therapy is initiated, periodic assessments are needed to identify progress. The goals of therapy are to improve cardiac output, because that will lead to improvement in the patient's functional capacity and quality of life, and to decrease vascular resistance, which is the determinant of right ventricular performance, he said.

For patients who do not improve on monotherapy, an option increasingly being explored is combination therapy.

"A fundamental question today is what model we should use," said Dr. Palevsky, who is also chief of pulmonary, allergy, and critical care at Penn Presbyterian Medical Center, Philadelphia.

"One model is the one used for systemic hypertension, where you give one therapy, assess the response, and if that's not doing what you want, add a second drug, and if that's not enough add a third drug. The alternative is a cancer chemotherapy model, where you give the patient the best therapy up front aiming for remission, and then down-titrate to maintenance therapy," he said.

Preliminary data from a U.S. trial comparing inhaled iloprost plus oral bosentan with bosentan alone suggest that the current stepwise approach might be problematic, he said.

The multicenter, double-blinded trial randomized 67 adults with PAH to 12 weeks of treatment with the endothelin receptor antagonist alone or in combination with the inhaled prostacyclin derivative.

Although this was primarily a safety study, the trial found that the combination group had an improvement in the 6-minute walk by a placebo-corrected 26 m (Am. J. Respir. Crit. Care Med. 2006;174:1257-63).

Moreover, one-third of the patients who had the combination improved by one functional class, Dr. Palevsky said.

In the open-label extension phase of the trial, 60 patients received the combination and were followed for 12 months. "What was concerning about this was that after the patients previously receiving monotherapy began also receiving iloprost they didn't catch up, raising the question of whether we need to be more aggressive in early treatment," he said.

A similar study undertaken in Europe showed contrasting results. A total of 40 patients were randomized to receive bosentan alone or in combination with iloprost for 12 weeks, but an interim analysis found that the primary end point, the 6-minute walk test, was not met, and the trial was terminated (Eur. Respir. J. 2006;28:691-4).

Several other studies are underway investigating other combinations and addressing other questions, such as whether patients with early PAH can benefit from treatment. Newer agents also are being evaluated. "Whether any of the alternatives under investigation will supplant our current therapies is not yet known, but it's our dream. I'd love to be able to see the CADD pump in the Smithsonian before I retire," Dr. Palevsky said, referring to the continuous infusion pump used with epoprostenol. ■