Bosentan Slows Progression in Class II PAH

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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 (PAH) "as soon as possible after the diagnosis is made because the majority of patients with PAH are in functional class II or III; the majority of PAH patients need treatment [with bosentan] according to these data," 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."

EARLY showed that in a pure cohort of class II patients, early treatment may delay PAH progression.

DR. RUBIN

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.

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 (in about 17%), connective tissue disease (in about 18%), or HIV infection (in about 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 treatment, the change from baseline in pulmonary vascular resistance, one of two primary end points, was increased by about 7% among 88 evaluable patients in the placebo group, and was decreased by about 16% in 80 patients in the bosentan group. The overall effect of bosentan treatment 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-meter 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," said Dr. Galiè. 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 tolerat-

ed, 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 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 enrolled 157 patients who had a specific, relatively common form of PAH, chronic thromboembolic pulmonary hypertension (CTEPH), which was inoperable or recurrent. The results 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.

The Bosentan Effects in Inoperable Forms of CTEPH (BENEFIT) study randomized patients to treatment with 62.5 mg bosentan b.i.d for 4 weeks, followed by 125 mg b.i.d. for 12 weeks or placebo. Their average age was 63 years. Bosentan was linked with a significant, 24% reduction in peripheral vascular resistance in 66 evaluable patients, compared with 71 placebo patients. Treatment also significantly boosted cardiac index, and cut NT-proBNP levels and dyspnea scores. Bosentan treatment had no significant effect on 6-minute walk distance.

Another study assessed the acute hemodynamic effect of a single, 25-mg dose of sildenafil in 44 patients with PAH already on chronic bosentan treatment. The results showed that the single sildenafil dose was safe, and after 60 minutes led to a significant drop in pulmonary vascular resistance, total pulmonary resistance, pulmonary artery pressure, and cardiac output.

The third study examined the pharmacokinetics of a new formulation of bosentan designed for use in children. Results from 35 patients aged 2-11 years showed that the formulation led to reasonable serum levels and a good safety profile.

"New drugs such as bosentan have dramatically improved outcomes for patients with pulmonary arterial hypertension. It is gratifying to see extension of the research into patients with early disease and in children," commented 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. ■