

# PAH Guidelines Reflect Data on Newest Drugs

BY NANCY WALSH  
New York Bureau

Updated clinical practice guidelines for the medical management of pulmonary arterial hypertension from the American College of Chest Physicians reflect findings from several recent clinical trials as well as the additional drugs that have been approved since the previous guidelines were issued in 2004.

The guidelines include an evidence-based, updated treatment algorithm intended to assist physicians in decision making (Chest 2007;131:1917-28).

Providing new data were two "important" studies that demonstrated survival benefits in patients treated with bosentan, which binds to both endothelin receptors (ET<sub>A</sub> and ET<sub>B</sub>), according to lead author Dr. David B. Badesch of the University of Colorado Health Sciences Center, Denver.

In the first study, 169 patients (aged 13-80 years) with class III or IV PAH were treated with bosentan as first-line therapy. Survival was 96% at 12 months and 89% at 24 months, in contrast to predicted survival rates from the earlier National Institutes of Health registry of 69% and 57%, respectively (Eur. Respir. J. 2005;25:244-9).

In the second study, survival in 139 patients treated with bosentan was compared with historical data from 346 patients who had been treated with epoprostenol. Survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated group, and

91% and 84% in the epoprostenol-treated group (Thorax 2005;60:1025-30).

Baseline characteristics of the patients suggested that the epoprostenol patients had more severe disease. But Cox regression analyses adjusting for baseline factors showed a greater risk of death in the epoprostenol group (hazard ratio 2.2).

Bosentan also has now been evaluated in children with PAH associated with congenital heart disease or connective tissue disease. In a retrospective study, 86 children were treated with bosentan with or without concomitant epoprostenol or treprostinil. WHO functional class improved in 46% of patients and was unchanged in 44%, and survival estimates at 1 and 2 years were 98% and 91% (J. Am. Coll. Cardiol. 2005;46:697-704).

Another recent study included 245 patients (ranging in age from 12 years to 78 years) who received bosentan, placebo, or one of two doses of a selective ET<sub>A</sub> endothelin receptor antagonist, sitaxsentan. At week 18, patients receiving the higher dose of sitaxsentan (100 mg/day) had significant improvements on a 6-minute walk test, compared with those receiving placebo. The incidence of elevated transaminases was 6% in the placebo group, 5% in the sitaxsentan low-dose (50 mg/day)

group, 3% in the high-dose sitaxsentan group, and 11% in the bosentan group (J. Am. Coll. Cardiol. 2006;47:2049-56).

Sitaxsentan remains investigational in the United States, but has been approved for use in Europe and Canada.

A second selective ET<sub>A</sub> endothelin receptor antagonist, ambrisentan, was evaluated in a double-blind, dose-ranging study that included 64 adult patients with PAH. They were randomized to receive 1 mg, 2.5 mg, 5 mg, or 10 mg of ambrisentan orally once daily for 12 weeks. The 6-minute walk test im-

proved significantly for all groups, with a mean increase from baseline of 36.1 meters. Improvements also were seen in WHO functional class, Borg dyspnea index, and cardiac index (J. Am. Coll. Cardiol. 2005;46:529-35).

Adverse events were mild, with elevated serum aminotransferase exceeding three times the upper limit of normal seen in 3.1% of patients. This drug was recently approved for class II and class III PAH in the United States.

The phosphodiesterase inhibitor sildenafil also is now approved for the treatment of all classes of PAH in a dosage of 20 mg three times daily. The drug was evaluated in a double-blind study that randomized 278 patients (mean age 50 years)

to placebo or 20, 40, or 80 mg three times daily for 12 weeks.

Improvements were seen in the 6-minute walk test in all groups, with placebo-corrected treatment effects being +13%, +13.3%, and +14.7% in the 20-, 40-, and 80-mg groups, respectively. The incidence of clinical worsening did not differ significantly between the placebo and sildenafil groups. Side effects included flushing, dyspepsia, and diarrhea.

In summarizing the treatment options, the authors noted that for patients in functional class II, the only current recommended drugs are sildenafil and subcutaneous and intravenous treprostinil, and suggested that sildenafil may be the first choice for most patients because of ease of administration and relative efficacy.

For patients in functional class III, five drugs are available: bosentan, sildenafil, intravenous epoprostenol, inhaled iloprost, and subcutaneous or intravenous treprostinil. For those with early class III disease, oral bosentan or sildenafil may be used, with the choice reflecting relative toxicities. For patients with more advanced disease, prostanoid therapy may be needed.

All the available agents are approved for patients with class IV PAH. However, the authors wrote, "[we] strongly encourage IV epoprostenol as the treatment of choice for these most critically ill patients. IV epoprostenol has a rapid and predictable onset of action, and most experts are familiar with how to titrate this drug in the acute setting."

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## Peripartum Cardiomyopathy Improved With Bromocriptine

BY BRUCE JANCIN  
Denver Bureau

VIENNA — The dopamine agonist bromocriptine shows considerable promise for the treatment of peripartum cardiomyopathy, Dr. Olaf Forster said at the annual congress of the European Society of Cardiology.

"The results obtained by the addition of bromocriptine to standard heart failure treatment in this study are encouraging. Bromocriptine may represent a novel therapeutic approach in the treatment of peripartum cardiomyopathy, but the data need to be considered as preliminary," according to Dr. Forster of the University of the Witwatersrand, Johannesburg, South Africa.

The hallmark of peripartum cardiomyopathy (PPCM) is onset of left ventricular failure between 1 month before and 5 months after delivery. The highest rates of PPCM in the world are reported in South Africa. "We get two or three new patients per week in Soweto," said Dr. Forster, who is with the university's cardiovascular research unit at the Chris Hani Baragwanath Hospital, Soweto.

Treatment of PPCM involves standard heart failure medications and firm advice to avoid further pregnancies. A subsequent pregnancy can be fatal; half of women who become pregnant again after a first episode of PPCM experience long-term worsening of heart failure, whereas the other half return to their normal prepregnancy left ventricular systolic function.

Dr. Forster reported on 16 indigenous black women ages 26-39 with PPCM who presented with a subsequent pregnancy 1-6 years following their index PPCM pregnancy. The first six women—the control group—didn't receive bromocriptine because their pregnancies occurred before the South African team learned of evidence from German studies in knockout mice suggesting that the drug might be beneficial in PPCM. The next 10 patients received bromocriptine at 2.5 mg b.i.d. for 2 months beginning 4 hours post delivery. This was the first study of the drug in human PPCM.

All 16 patients were on a diuretic and  $\beta$ -blocker during pregnancy, with an ACE inhibitor added post partum.

The mean left ventricular ejection fraction in controls was 44% at baseline, declining to 36% at 1 month post partum and to 25% 3 months post partum. In contrast, the baseline ejection fraction was 51% in the bromocriptine-treated group, dropping to 43% 1 month post partum, and rebounding to 55% by 3 months post partum.

At 3 months post partum, 2 of 6 controls were dead of heart failure, compared with none of the 10 women who received bromocriptine.

Bromocriptine had no side effects, but some women on the prolactin inhibitor were quite disturbed that they couldn't breast feed, according to Dr. Forster.

In the STAT3 female knockout mouse model of PPCM, enhanced postpartum oxidative stress results in cathepsin D-facilitated cleavage of the 23-kd form of prolactin into its 16-kd form, which is proapoptotic and antiangiogenic. This short-form prolactin disrupts endothelial cell function and promotes vasoconstriction, resulting in impaired cardiac microcirculation, increased cardiac apoptosis, and reduced postpartum survival.

Bromocriptine prevents PPCM in this model.

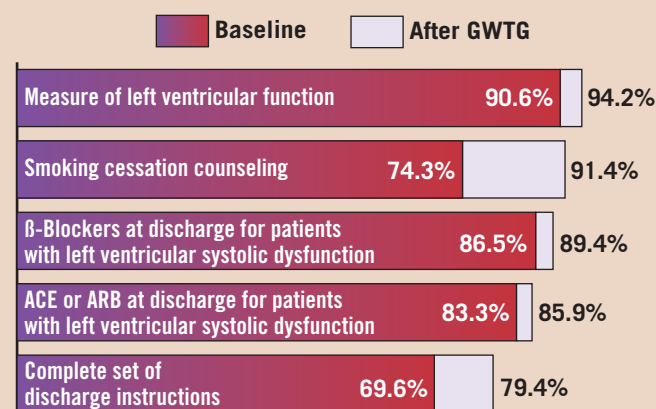
Session cochair Dr. Robert Califf, vice-chancellor for clinical research, director of the Translational Medicine Institute, and professor of medicine at Duke University, Durham, N.C., called the clinical results encouraging, but wondered why the investigators hadn't mounted a randomized trial. Dr. Forster replied that

the risks posed by subsequent pregnancy in women with PPCM are so great that he and his coworkers believe it would be unethical to deny them bromocriptine. "The risk is simply too high—and we can see that it works," he explained.

However, a randomized trial is ongoing in women experiencing a first episode of PPCM, Dr. Forster added.

### DATA WATCH

#### Results of Get With the Guidelines Heart Failure Program in 2006



Note: Based on data for 35,576 patients in key performance measures. Source: American Heart Association