Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 52, No. 25, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.08.059

Bosentan for Treatment of Inoperable Chronic Thromboembolic Pulmonary Hypertension

BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a Randomized, Placebo-Controlled Trial

Xavier Jaïs, MD,* Andrea M. D'Armini, MD,† Pavel Jansa, MD,‡ Adam Torbicki, MD,§ Marion Delcroix, MD,‖ Hossein A. Ghofrani, MD,¶ Marius M. Hoeper, MD,# Irene M. Lang, MD,** Eckhard Mayer, MD,†† Joanna Pepke-Zaba, MD,‡‡ Loïc Perchenet, PhD,§§ Adele Morganti, MSc,§§ Gérald Simonneau, MD,* Lewis J. Rubin, MD,‖‖ for the BENEFiT Study Group

Clamart, France; Pavia, Italy; Prague, Czech Republic; Warsaw, Poland; Leuven, Belgium; Giessen, Hannover, and Mainz, Germany; Vienna, Austria; Cambridge, United Kingdom; Allschwil, Switzerland; and La Jolla, California

Objectives Our goal was to investigate the effect of treatment with the oral dual endothelin receptor antagonist bosentan on the hemodynamics and exercise capacity of patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Background CTEPH is characterized by vascular obstruction and remodeling, leading to increased pulmonary vascular resistance (PVR). Although pulmonary endarterectomy (PEA) is potentially curative, medical therapy is needed in patients with inoperable disease or persistent/recurrent pulmonary hypertension after PEA.

Methods The BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) study was a double-blind, randomized, placebo-controlled study in CTEPH including patients with either inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA (>6 months after PEA). Independent coprimary end points were change in PVR as a percentage of baseline and change from baseline in 6-min walk distance after 16 weeks of treatment with bosentan or placebo. Secondary end points included change from baseline in World Health Organization functional class and other hemodynamic parameters.

Results One hundred fifty-seven patients were enrolled and randomized: 80 to placebo, 77 to bosentan. A statistically significant treatment effect (TE) of bosentan over placebo on PVR was demonstrated: −24.1% of baseline (95% confidence interval [CI]: −31.5% to −16.0%; $p < 0.0001$). Total pulmonary resistance (TE: −193 dyn·s·cm^{-5}; 95% CI: −283 to −104 dyn·s·cm^{-5}; $p < 0.0001$) and cardiac index (TE: 0.3 l·min^{-1}·m^{-2}; 95% CI: 0.14 to 0.46 l·min^{-1}·m^{-2}; $p = 0.0007$) improved. Mean TE on 6-min walk distance was +2.2 m (95% CI: −22.5 to 26.8 m; $p = 0.5449$). Bosentan treatment was well tolerated.

Conclusions This study demonstrated a positive TE of bosentan on hemodynamics in this patient population. No improvement was observed in exercise capacity. Further trials are needed to define the role of medical therapy in patients with CTEPH (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension; NCT00313222). (J Am Coll Cardiol 2008;52:2127–34) © 2008 by the American College of Cardiology Foundation

From the *Antoine Béclère Hospital, Clamart, France; †Division of Cardiac Surgery, St. Matteo Hospital, University of Pavia School of Medicine, Pavia, Italy; ‡Charles University, 1st Faculty of Medicine, 2nd Medical Department–Clinical Department of Cardiology and Angiology, Prague, Czech Republic; §Department of Chest Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland; ‖Department of Pulmonology, University Hospital Gasthuisberg, Leuven, Belgium; ¶University of Giessen Lung Center, Giessen, Germany; #Hannover Medical School, Hannover, Germany; **Medical University of Vienna, Vienna, Austria; ††Catholic Academic Hospital, Mainz, Germany; ‡‡Papworth Hospital, Cambridge, United Kingdom; §§Actelion Pharmaceuticals Ltd., Allschwil, Switzerland; and the ‖‖University of California, San Diego, La Jolla, California. This study was funded by Actelion Pharmaceuticals. Dr. Jaïs has received consulting fees, speaking fees, and honoraria from Actelion and GlaxoSmithKline. Dr. D'Armini has received consulting fees for service as a Steering Committee member for Actelion Pharmaceuticals. Dr. Jansa has received honoraria from Actelion Pharmaceuticals and fees for consultancies from Actelion, Pfizer, GlaxoSmithKline, and AOP Orphan Pharmaceuticals. Dr. Torbicki has received speaker fees and honoraria for consultations from Actelion, Bayer-Schering, and GlaxoSmithKline. Dr. Delcroix has received consulting fees and research grants from Actelion. Dr. Ghofrani has received honoraria from Actelion, Bayer, Encysive Pharmaceuticals, Ergonex, Pfizer, and GlaxoSmithKline. Dr. Hoeper

JACC Vol. 52, No. 25, 2008
December 16/23, 2008:2127–34

Abbreviations and Acronyms

CI = confidence interval
CTEPH = chronic thromboembolic pulmonary hypertension
ET = endothelin
mPAP = mean pulmonary arterial pressure
NT-proBNP = N-terminal pro-brain natriuretic peptide
PAH = pulmonary arterial hypertension
PCWP = pulmonary capillary wedge pressure
PEA = pulmonary endarterectomy
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
WHO = World Health Organization
6MWD = 6-min walk distance

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition characterized by chronic organized thrombi that obstruct the pulmonary vessels, leading to increased pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH), and right heart failure (1,2). Although obstruction of pulmonary arteries is recognized as the inciting event, promoting increased PVR and progressive PH, small-vessel arteriopathy is believed to appear in the course of the disease and to contribute to the progression of hemodynamic and symptomatic decline.

The incidence of CTEPH is difficult to assess and may have been underestimated in the past. Recently, in a single-center, prospective, longitudinal study, the cumulative incidence of CTEPH after pulmonary embolism was reported to be 3.8% at 2 years (3).

Pulmonary endarterectomy (PEA) is the treatment of choice, offering immediate hemodynamic benefits and providing a potential cure for many patients (4). However, PEA is not possible for 10% to 50% of patients (inoperable CTEPH), due to either distal pulmonary vascular obstruction that is surgically inaccessible or significant comorbidities thought to be associated with unacceptably high risk (5). Furthermore, in CTEPH patients with disease amenable to surgery, approximately 10% to 15% of patients have residual PH (mean pulmonary arterial pressure [mPAP] >25 mm Hg) (6) after PEA (persistent/recurrent post-operative PH) (7). In these situations, medical treatments may, therefore, be useful. However, there is currently no approved medical therapy for inoperable CTEPH or patients with persistent/recurrent PH post-PEA.

Untreated, CTEPH has a poor prognosis, with over one-half of patients with mPAP >50 mm Hg not surviving beyond 1 year after diagnosis (8). Pulmonary hemodynamics and PVR are believed to be critical, as a significant reduction after surgery is associated with increased survival, and high pre-operative values carry a significant risk of surgical mortality (9,10).

Histopathologic studies of vascular changes in CTEPH have identified vascular lesions similar to those seen in idiopathic pulmonary arterial hypertension (PAH) (11). As in PAH, endothelin (ET)-mediated vascular remodeling has been demonstrated in animal models of CTEPH (12), and increased ET levels and ET_B receptor expression have been observed in CTEPH patients (13). For these reasons, the dual ET receptor antagonist, bosentan, which is effective in the treatment of idiopathic PAH as well as PAH associated with other conditions (14–17), appears to be a potential treatment option for inoperable or persistent/recurrent CTEPH. In addition, several uncontrolled trials in CTEPH have suggested that bosentan is effective in improving exercise capacity and hemodynamics (18–20), warranting further study.

The BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) trial was designed to demonstrate whether bosentan improves PVR and/or exercise capacity (independent coprimary end points) at week 16 in patients with inoperable or persistent/recurrent CTEPH. Secondary objectives were to evaluate the effect of bosentan on time to clinical worsening, World Health Organization (WHO) functional class and hemodynamics, and to evaluate the safety and tolerability of bosentan in this patient population.

Methods

Study design. In this prospective, multicenter, double-blind, placebo-controlled, parallel-group study, patients were randomized 1:1 to receive bosentan or placebo for 16 weeks. All patients were given an initial dose of 62.5 mg twice a day for 4 weeks, increasing to the target dose of 125 mg twice a day thereafter. Patients weighing <40 kg were maintained at 62.5 mg twice a day throughout the study. This study was conducted in full compliance with the principles of the most recent amendment to the Declaration of Helsinki and with the laws and regulations of the countries in which the research was conducted. All patients gave their informed consent. The protocol and any material provided to the patient were reviewed and approved by the appropriate independent ethics committee or institutional review board before the study was started.

Main inclusion and exclusion criteria. This study included symptomatic PH patients in WHO functional class II, III, or IV who were 18 to 80 years of age with a diagnosis of CTEPH, as demonstrated by ventilation/perfusion lung

has received speaker fees and honoraria for consultations from Actelion Pharmaceuticals, Encysive Pharmaceuticals, Pfizer, and Bayer-Schering. Dr. Lang has received honoraria from Actelion, Bayer-Schering, Pfizer, AstraZeneca, GlaxoSmithKline, AOP Orphan Pharmaceuticals, and Encysive Pharmaceuticals, and grant support from Actelion Pharmaceuticals, the EU, and the Austrian government. Dr. Mayer has received speaker fees from Actelion and Bayer. Dr. Pepke-Zaba has received honoraria from Actelion, Encysive Pharmaceuticals, Pfizer, GlaxoSmithKline, and Bayer-Schering, and also holds educational grants funded in part or whole from Actelion, Lung Rx, Pfizer, and Schering. Dr. Simonneau has received honoraria for consultations and/or lecture fees from Pfizer, GlaxoSmithKline, Actelion, Lilly, United Therapeutics, and Bayer, and industry sponsored grants from Pfizer, GlaxoSmithKline, Actelion, Lilly, and United Therapeutics. Dr. Rubin has received consulting fees for service as a Steering Committee member and advisor, and honoraria for lectures from Actelion. Dr. Perchenet and Adele Morganti are employees of Actelion Pharmaceuticals Ltd. Valerie V. McLaughlin, MD, served as Guest Editor for this article.

Manuscript received May 22, 2008; revised manuscript received July 23, 2008, accepted August 12, 2008.