CHEST

Original Research

PULMONARY HYPERTENSION

Conversion to Bosentan From Prostacyclin Infusion Therapy in Pulmonary Arterial Hypertension*

A Pilot Study

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Study objectives: **We assessed the efficacy of bosentan in transitioning from prostacyclin infusions in patients with pulmonary arterial hypertension (PAH).**

Methods: **Twenty-two PAH patients were recruited from five PAH centers if they had been clinically stable while receiving therapy with IV epoprostenol or subcutaneous treprostinil for at least 3 months. Patients were observed in an open-label prospective trial while bosentan was added to therapy, and then epoprostenol or treprostinil were tapered after 2 months.**

Results: **Ten of the 22 patients were transitioned off prostacyclin infusion therapy after a mean (± SEM) duration of 6.1 ± 1.2 months. Of those patients, seven patients have continued not receiving prostacyclin infusion therapy for a mean duration of 17.7 ± 5.3 months, with no significant changes in pulmonary artery (PA) pressure estimated by echocardiography, World Health Organization (WHO)/New York Heart Association (NYHA) functional class, 6-min walk distance (6MWD), or Borg dyspnea score. The conditions of three patients deteriorated, necessitating the resumption of prostacyclin therapy, and two patients subsequently died. Twelve patients failed to transition or even lower the prostacylin infusion rate and had worsening of their WHO/NYHA functional class and estimated systolic PA pressures, and had a trend toward deterioration in their mean 6MWD (294 ± 41 to 198 ± 34 m, respectively; p = 0.2). Of these, two patients subsequently died. The baseline characteristics of those who transitioned successfully vs those who transitioned unsuccessfully were a lower prostacyclin infusion rate, and less severe elevations in the mean and estimated systolic PA pressures.**

Conclusion: **Transitioning from therapy with prostacyclin to bosentan is possible in some PAH patients, mainly in those receiving lower prostacyclin doses and having less pulmonary hypertension at baseline. Careful patient selection and close interim monitoring is needed because the conditions of patients can deteriorate, and they may not respond to the resumption of therapy with prostacyclin.** ***(CHEST 2006; 130:1471–1480)***

Key words: bosentan; epoprostenol; pulmonary arterial hypertension; transitions; treprostinil

Abbreviations: CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PGI_2 = prostaglandin I_2; PVR = pulmonary vascular resistance; WHO = World Health Organization; 6MWD = 6-min walk distance

Pulmonary arterial hypertension (PAH) is an uncommon disease that is characterized by a progressive increase in pulmonary vascular resistance (PVR) leading to right ventricular failure and death.[1] PAH occurs as an idiopathic process or in association with a variety of disease processes. The pathogenesis is unknown but is thought to involve an imbalance between vasoconstrictor and vasodilator mediators, favoring vasoconstriction and predisposing the patient to vessel wall thickening.[2–4]

Therapies that are aimed at restoring the vasodilator/vasoconstrictor balance by the infusion of pros-

tacyclin analogues such as epoprostenol improve pulmonary hemodynamics, functional status, and survival.[5,6] However, this therapy is complicated, requiring permanent placement of a tunneled central venous catheter and posing an ever-present risk of line infection.[7] Furthermore, abrupt discontinuation of the infusion can be life-threatening because of the short half-life of the drug.[7] Treprostinil, which is a prostacyclin analog with a longer half-life than epoprostenol, can be given subcutaneously,[8] providing therapy with greater convenience and safety than that with epoprostenol, but most patients are troubled by pain at the infusion site. Treprostinil can also be administered IV, offering convenience and safety advantages over IV epoprostenol, but line sepsis remains a threat.[9] Thus, the transition from prostacyclin infusion to oral therapy is an appealing option for many patients with PAH.

Bosentan, which is an orally active nonselective endothelin receptor antagonist, improves the 6-min walk distance (6MWD), pulmonary hemodynamics, and functional status, and delays the time to clinical worsening in patients with class III or IV PAH patients compared to placebo.[10] Few studies[11,12] have examined the possibility that patients receiving infusion therapies can be transitioned to more convenient and less complicated oral therapies such as with bosentan. Even with the lowering of the prostacyclin dose, such an intervention would cut down on expense, reduce the side effects, and minimize the risks of overdosage and high cardiac output failure that are inherent with prostacyclin infusion. Moreover, no characteristics have been identified that can predict the success or failure of therapy transitioning. In this pilot study, we asked whether adding bosentan to prostacyclin infusion therapy would (1) permit a lowering of the prostacyclin dose with the maintenance of functional capacity and (2) allow long-term complete transitioning in some patients. We also sought to identify patient characteristics that would predict successful transitioning.

Materials and Methods

Patients

The study was approved by the institutional review boards at all five participating PAH centers (*ie*, Tufts-New England Medical Center, Boston Medical Center, Rhode Island Hospital/Brown University, Massachusetts General Hospital, and Temple University) and was overseen by a data safety monitoring board. Patients with PAH receiving therapy either epoprostenol or treprostinil by continuous infusion were offered entry into the trial for potential transitioning to therapy with oral bosentan, and enrolled patients gave written informed consent. Patients who were deemed to be eligible for the study were over age 18 years, had experienced clinically stable PAH (defined as stable symptoms and no evidence of heart failure) for at least 3 months, had a stable World Health Organization (WHO)/New York Heart Association (NYHA) functional score, had experienced a $<10\%$ change in 6MWD, and had undergone no changes in their prostacyclin dose for at least the previous month. Patients needed to have had PAH confirmed on a prior right heart catheterization, as determined by a mean pulmonary artery (PA) pressure of ≥ 25 mm Hg at rest and a PA wedge pressure of ≤ 15 mm Hg. In addition to idiopathic PAH, patients with PAH associated with connective tissue disease, congenital heart disease, sarcoidosis, or HIV were also eligible to be enrolled in the study.

Patients were excluded from the study if they were receiving therapy with cyclosporine A or glyburide, had a history of cirrhosis or elevated baseline levels of transaminases more than three times the upper limit of normal, worsening signs or symptoms of pulmonary hypertension (defined as escalating dyspnea, light-headedness, chest pain, WHO/NYHA functional score, or prostacyclin doses, or signs of worsening right heart failure), were receiving another investigational drug, had a current or planned pregnancy, or were nursing. Women were eligible to participate in the trial if they were surgically sterile, at least 1 year postmenopausal, or were using nonhormonal birth control and had a negative urine or serum pregnancy test result at baseline. Patients were enrolled in the study between June 2002 and January 2004.

Transition Process

Enrolled patients were started on therapy with bosentan, 62.5 mg bid for a month, after which the dose was increased to 125 mg bid, unless the liver function test results increased by more than threefold or the patient had another serious adverse reaction. The decrease in the dose of epoprostenol or trepostinil was started on an outpatient basis 8 weeks after the initiation of bosentan therapy, based on the reported time to maximal effect.[10] The prostacyclin infusion rate was decreased by 2

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