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Scientific Update™

From Endothelin to Endothelin Receptor Antagonism: An Innovative Approach to Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease. Although relatively rare, PAH is occurring with increasing frequency in certain patient populations, including those with connective tissue disease and congenital heart disease. Until recently, the treatment options for PAH were relatively limited. While the etiology of PAH may be multi-factorial, it is evident that the endothelium-derived peptide, endothelin, is an important mediator in the development and progression of PAH; therefore, endothelin is a crucial target in the treatment of these patients. Bosentan is an oral dual endothelin receptor antagonist that has been shown to be effective in the treatment of PAH and evidence supporting its effectiveness has been reviewed in a previous issue of *Cardiology Scientific Update*. In this issue, clinical approaches to the treatment of PAH, including new long-term follow-up data and potential novel applications of bosentan in the treatment of PAH will be discussed.

The role of the cardiologist in the diagnosis and management of PAH

PAH is a rare, progressive, and lethal disease.[1] In the diagnostic classification of pulmonary hypertension that was proposed by the World Health Organization (WHO),[2] and recently updated at the 3rd World Symposium on Pulmonary Arterial Hypertension, PAH is sub-classified into idiopathic PAH, familial PAH, and PAH related to known etiologies such as connective tissue disease, congenital heart disease, HIV-related illnesses, and the use of anorexic agents. Irrespective of the etiology, PAH-related disorders share a number of common features, including proliferative and obstructive lesions in the small pulmonary arteries, *in situ* thrombosis, and characteristic plexiform lesions.[1,3] Until recently, only limited therapeutic options have been available for these patients.

The diagnosis of PAH can be challenging because early clinical symptoms (eg, dyspnea on exertion) can be nonspecific. As a result, PAH is often unsuspected and its diagnosis may be delayed for years after the onset of symptoms.[4] Even in symptomatic patients, specific ECG and radiographic signs may be absent. The definitive diagnosis of PAH still requires direct measurement of pulmonary artery pressure (PAP). A mean PAP >25 mm Hg at rest and >30 mm Hg with exercise has been proposed to be diagnostic of PAH.[4] Although echocardiography does not allow a definitive diagnosis of PAH, it has been shown to be a sensitive and specific diagnostic tool.[5] Perhaps its greatest application is in screening patients at high risk for developing PAH,[2] (eg, patients with scleroderma and other connective tissue disease, those infected with HIV, and relatives of patients with idiopathic PAH). A Doppler echocardiographic evaluation is also useful in PAH to assess the magnitude of right ventricular (RV) involvement. More recently, the Doppler right ventricular index (DRVI), also called the Tei index, a parameter that incorporates both systolic and diastolic performance of the RV, has been shown to independently predict mortality in patients with idiopathic PAH.[6]

RV involvement leads to increased circulating levels of various biochemical markers, including uric acid,[7] brain natriuretic peptide[8] and troponin T.[9] Levels of all of these markers have been shown to have independent prognostic values in patients with PAH. Eventually, combined Doppler-echocardiographic assessment and prognostic markers may allow for better staging of the disease, an optimal treatment strategy, as well as the need for invasive therapy (eg, transluminal atrial septostomy).

Endothelin: a new scientific era

Endothelin (ET) is a regulatory peptide that is synthesized by endothelial cells. It mediates key physiological functions in normal tissues, acting as a modulator of vasomotor tone, tissue differentiation, cell proliferation, and hormone production.[10,11] ET is present in low concentrations in the healthy state. During

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pathological conditions, when the ET system is activated, this peptide causes vasoconstriction of the systemic, renal, pulmonary, and coronary vasculatures.[11-14] ET also stimulates vascular smooth muscle and myocytes to induce hypertrophy[15] and is a mitogen for endothelial cells and fibroblasts.[16] Furthermore, ET induces fibrosis and is implicated in the development of inflammatory reactions.[17]

The actions of ET are mediated through binding of ET to receptors on the cell surface. In humans, 2 classes of ET receptor have been identified and characterized, namely type A (ET_A) and type B (ET_B) receptors.[18] Both of these receptor subtypes are likely involved in mediating the deleterious effects of ET in pathological conditions.[11,19,20] ET_A receptors are mainly located in vascular smooth muscle cells and myocytes, whereas ET_B receptors are found on smooth muscle cells, endothelial cells, and fibroblasts. ET_B receptors mediate release of prostacyclin and nitric oxide, but also play an important role in vasoconstriction, cell proliferation, fibrosis, and inflammation.[21]

ET has now been implicated as a mediator in several disease states, including pulmonary hypertension, connective tissue disease, interstitial lung disease, and heart failure.[22-26] Endothelin receptor blockade remains a promising approach in the treatment of various diseases. Indeed, the progression of research on the ET system has been one of the most rapid in history, with the initial discovery of the peptide in 1998,[13] the first report of a synthetic oral non-peptide receptor antagonist in 1993,[27] and the availability of the first ET receptor antagonist for clinical use in 2001.

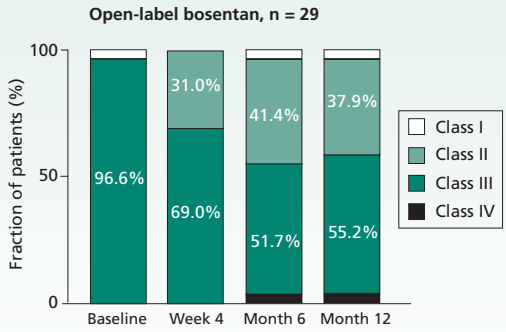
Endothelin receptor antagonism in PAH: From science to clinical practice

There is ample evidence supporting the role of ET in the pathophysiology of PAH.[28] Therefore, ET receptor antagonists have been investigated as a therapeutic approach. Bosentan is an orally active dual ET receptor antagonist that binds to both ET_A and ET_B receptors.[29] In animal models, bosentan has been shown to antagonize the deleterious effects of ET, resulting in vasodilation, and anti-trophic, anti-fibrotic, and anti-inflammatory effects.[30]

To date, there have been 2 double-blind, placebo-controlled, trials of bosentan in patients with PAH.[31-33] Both were reviewed in a previous issue of *Cardiology Scientific Update*. In brief, bosentan improved the 6-minute walking distance in both studies. In the Bosentan Randomized Trial Endothelin Antagonist Therapy-1 (BREATHE-1) study,[32,33] bosentan also improved the Borg dyspnea index and WHO functional class and increased time to clinical worsening. These findings are particularly important since the 6-minute walk test and WHO functional class have been identified as independent predictors of survival in PAH.[5,34] BREATHE-2 was a smaller study, designed to assess the effect of bosentan versus placebo in PAH patients treated with epoprostenol. The results have been reported thus far in abstract form[35] and demonstrate a trend towards improvement with bosentan in hemodynamic parameters, exercise capacity, and WHO functional class. Importantly, the combination of bosentan and epoprostenol appeared to be well-tolerated.

A recently published Doppler echocardiographic substudy of BREATHE-1 has added mechanistic insights to the beneficial effects of bosentan.[36] In this study of 85 patients, bosentan was shown to improve Doppler-derived cardiac index and reduce right and left ventricular end-diastolic area. Importantly, bosentan improved the Doppler right ventricular index, a prognostic indicator in patients with idiopathic PAH.[6] These findings are likely reflective of the favourable effect of bosentan in pulmonary vascular hemodynamics.

Figure 1: WHO functional class on long-term follow-up[37]



The baseline of the study is the beginning of the preceding study for ex-bosentan patients and the beginning of the open-label study for the ex-placebo patients. WHO functional class IV patients received epoprostenol.

Treatment beyond symptoms or the chance to make a difference

The major goal of any therapy, in addition to relieving symptoms, is to target the underlying mechanism of the disease in order to favourably alter its course. Until recently, treatment options for PAH have been quite limited. In the double-blind placebo-controlled trials mentioned above, bosentan was shown to improve hemodynamics, exercise capacity, and WHO functional class in adult patients with PAH.[31-33] Recently, an open-labeled extension of the preceding double-blind study evaluated 29 of the original 32 patients who received placebo or bosentan for 3 to 7 months. The benefits of bosentan were maintained for up to 12 months of open-label bosentan therapy (total exposure to bosentan, including double-blind therapy was 10±1 months).[37] At month 6, ex-bosentan patients who continued the therapy maintained the improvement in walking distance recorded at the end of the previous double-blind study, whereas ex-placebo patients improved their walking distance following open-label bosentan. Long-term bosentan therapy also improved WHO functional class (Figure 1). Overall, bosentan treatment was well tolerated and no patients died during the course of the study. Notwithstanding the limitations associated with an open-label design, these data suggest that long-term treatment with bosentan is safe and likely has sustained benefits on exercise capacity and hemodynamics in patients with PAH.

Historically, the prognosis of patients with idiopathic PAH has been poor. Data from the National Institutes of Health (NIH) registry, as well as from series of patients treated with intravenous epoprostenol, reveal a 3-year survival of ≥50% (Figure 2).[5,38,39] In

Figure 2: Survival of patients with pulmonary arterial hypertension

	Survival (%) at		
	1 year	2 years	3 years
NIH registry[5]	68%	—	48%
On epoprostenol[38]	88%	76%	63%
On epoprostenol[39]	85%	70%	63%

Figure 3: Predicted survival with bosentan based on NIH registry data[40]

	Survival (%) at 1 year	2 years	3 years
Bosentan-treated patients (N = 169)			
Patients at risk	163	113	16
Survival			
Observed	96%	89%	86%
Predicted	69%	57%	48%

a recent, unpublished, retrospective analysis, survival data were collected for 169 patients with idiopathic PAH who received bosentan in the double-blind study or switched from placebo to bosentan in the open-label extension studies.[40] Survival estimates were made using the Kaplan-Meier method and compared with predicted survival based on NIH registry data (Figure 3). Comparison with historical controls revealed a significant improvement in the survival of bosentan-treated patients. Furthermore, a 6-minute walk distance test that was <359 m or a WHO functional class IV at baseline were predictive of a poor prognosis. In a rare and lethal disease such as PAH, conducting a randomized placebo-controlled trial evaluating hard outcomes such as survival will be exceedingly difficult. Nevertheless, the totality of efficacy and survival data to date appear to support the use of bosentan as first-line treatment in patients with PAH.

PAH related to congenital heart disease: a challenge

Congenital heart disease (CHD), which is characterized by various aberrant intracardiac flow patterns as a result of inborn structural defects, is often accompanied by PAH. Elevated circulating levels of ET have been demonstrated in CHD patients with increased pulmonary blood flow when compared to healthy subjects.[41-43] ET also likely plays a role in pre- and post-operative pulmonary vascular pathology and its clinical course in patients with CHD.[44] Accordingly, there is sound rationale for exploring the clinical utility of endothelin receptor antagonists in these patients.

As discussed in a previous issue of *Cardiology Scientific Update*, the oral dual ET receptor antagonist bosentan has significant benefits in adult patients with PAH, including improvements in hemodynamic parameters, WHO functional class, and the time to clinical deterioration.[31-33] Effects of bosentan have recently been evaluated in pediatric patients with either idiopathic PAH or PAH related to CHD in the Bosentan Randomized Trial Endothelin Antagonist Therapy-3 (BREATHE-3) study.[45] Nine pediatric patients with PAH were enrolled and stratified for body weight and epoprostenol use. Patients weighing between 10 and 20 kg, between 20 and 40 kg, or >40 kg received a single dose of 31.25, 62.5, or 125 mg, respectively, on day 1, followed by 4 weeks of treatment with the initial dose. The dose was then up-titrated to the target dose (31.25, 62.5, or 125 mg twice daily). Pharmacokinetic and hemodynamic parameters were obtained at baseline and after 12 weeks of treatment. The covariates of body weight, gender, age, and the use of epoprostenol, had no significant effect on the pharmacokinetics of bosentan. Bosentan produced hemodynamic improvement in these patients and was well-tolerated. At 12 weeks, the mean change from baseline in mean pulmonary artery pressure was -8.0 mm Hg and the change in the pulmonary vascular resistance index was -300 dyne x s x m^2/cm^5. These preliminary data therefore indicate that the pharmacokinetics and tolerability of bosentan in pediatric patients are similar to those in adult patients and that the applied dosing regimens may be appropriate to treat pediatric patients.

Figure 4: Bosentan in Eisenmenger syndrome: pilot data

- Open label study of 12 weeks

Key results

- 6/10 patients 41±5 years of age have completed the protocol so far
- No major adverse events
- No rise in liver enzymes
- At 3 months
  - All but one patient "feels better", none worse
  - O_2 saturation increased from 80.5±5.2 to 84.3±5.6%
  - 6-min walk distance increased from 281±115 m to 375±99 m

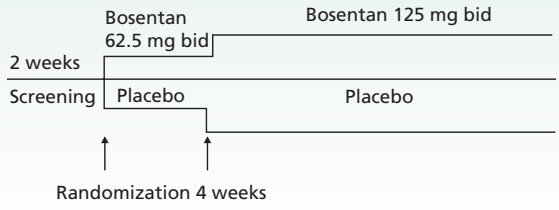
Eisenmenger syndrome

Eisenmenger syndrome represents the most severe form of PAH secondary to CHD. Continued exposure to high shear stress from a left-to-right shunt causes an increase in pulmonary vascular resistance to systemic levels, resulting in bi-directional and right-to-left shunting. Patients frequently develop cyanosis, secondary erythrocytosis, experience exertional dyspnea, and have overall reduced survival. Worsening symptoms, age, complex defects, blood creatinine level, right ventricular dysfunction, and non-cardiac surgery adversely affect the prognosis.[46] However, selected patients with Eisenmenger syndrome can survive to the seventh decade with meticulous care and protection from special risk. To date, treatment options include the use of prostacyclin, nitric oxide, phosphodiesterase inhibitors, and transplantation. However, these approaches are limited by the lack of long-term experience and uncertainty regarding patient selection and timing.[47-49] As patients with Eisenmenger syndrome are particularly sensitive to changes in blood pressure, they may be appropriate substrates for the use of ET receptor antagonists. Preliminary unpublished data from a pilot study of the use of bosentan in 10 patients with Eisenmenger syndrome, conducted in the Royal Brampton Hospital in London, UK, are shown in Figure 4. Importantly, there was no decline in oxygen saturation, the most feared complication of excessive vasodilation. Changes in the 6-minute walk distance and selected echocardiographic parameters appeared to be favourable.

This pilot study will be followed by BREATHE-5, a multicentre, randomized, double-blind, placebo-controlled trial. The study design is summarized in Figure 5. The primary endpoint is the effect of bosentan on systemic oxygen saturation. The key secondary endpoints include pulmonary vascular resistance, other hemodynamic parameters, exercise capacity, dyspnea, WHO functional class. and overall safety and tolerability. Enrollment is about to begin and results are anticipated in the fall of 2004.

In summary, endothelin receptor blockade using the dual ET receptor antagonist bosentan is now an established approach in the

Figure 5: BREATHE-5 study design



treatment of adults with PAH. Recent follow-up data from double-blind trials suggest that the beneficial effects of bosentan may be sustained for 36 months. Furthermore, preliminary data also suggest that bosentan may be beneficial in children with PAH secondary to congenital heart disease. Bosentan appears to be well-tolerated by adults with Eisenmenger physiology. Multi-centre, randomized, placebo-controlled trials in these patients are currently underway.

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