Chapter 14
Endothelin Receptor Antagonists

Josanna Rodriguez-Lopez and Richard N. Channick

Abstract Endothelin-1 (ET-1) is a potent vasoconstrictor and mitogen that is secreted by the endothelium. Pulmonary vascular expression of endothelin is increased in pulmonary hypertension and plasma levels correlate with the severity of disease. Several endothelin receptor antagonists (ERAs) have been developed and are available for the treatment of pulmonary arterial hypertension (PAH). These drugs have been shown to be effective at improving functional capacity, decreasing pulmonary vascular resistance and delaying the time to clinical worsening and play an important role in the management of PAH. This chapter briefly reviews how the endothelin signaling pathway modulates pulmonary vascular function and describes its role in the pathogenesis of PAH. The major clinical trials responsible for the currently available ERAs are presented along with their findings and limitations. Recently, adopted treatment guidelines for the use of ERAs in the treatment of pulmonary hypertensive disease are discussed along with potential side effects and adverse reactions associated with the use of these drugs.

Keywords Endothelin • Endothelin-1 • Endothelin receptor • Endothelin receptor antagonist • Pulmonary hypertension • Pulmonary arterial hypertension

Abbreviations

6MWD	6-min Walk distance
CTEPH	Chronic thromboembolic pulmonary hypertension
ERA	Endothelin receptor antagonist
ET-1	Endothelin-1
ET-2	Endothelin-2
ET-3	Endothelin-3
ET_A	Endothelin receptor A
ET_B	Endothelin receptor B

J. Rodriguez-Lopez, M.D. • R.N. Channick, M.D. (✉)
Pulmonary and Critical Care Division, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114-2696, USA
e-mail: RCHANNICK@mgh.harvard.edu

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IPAH	Idiopathic pulmonary arterial hypertension
mPAP	Mean pulmonary artery pressure
NO	Nitric oxide
PAH	Pulmonary arterial hypertension
PPET-1	Preproendothelin
PVR	Pulmonary vascular resistance
TPR	Total pulmonary resistance

Endothelin

The endothelins are a family of 21-amino acid peptides that play a key role in the regulation of vascular tone. The first member of this family to be identified was endothelin-1 (ET-1), a 2,492 Da peptide with potent vasoconstrictor properties, isolated in 1988 by Yanagisawa et al. [1]. Two additional endothelin isopeptides, endothelin-2 (ET-2) and endothelin-3 (ET-3), were subsequently discovered [2].

Vascular endothelial cells are the major source of endothelin production in humans. However, endothelin is also produced in a wide range of additional cell types including bronchial epithelium, macrophages, cardiac myocytes, glomerular mesangial cells and glial cells, among others [3–6].

The discovery that endothelin-1 is expressed in pulmonary artery endothelial cells and its receptors are expressed in pulmonary artery smooth muscle cells, led to the development of endothelin receptor antagonists as a therapy for pulmonary arterial hypertension (PAH).

Endothelin Receptors

There are two distinct receptors for the endothelin family of peptides, endothelin receptor A (ETA) and endothelin receptor B (ETB). The endothelin receptors belong to the family of receptors connected to guanine nucleotide-binding (G) proteins [7]. ETA receptors are expressed on pulmonary vascular smooth muscle cells while ETB receptors are located on both pulmonary vascular endothelial cells and smooth muscle cells. When activated, the ETA receptor mediates vasoconstriction. The mechanism is thought to occur via G-protein-induced phospholipase C activation; 1,4,5-inositol triphosphate (IP3) formation; and the consequent release of Ca^{2+} from intracellular stores [7]. In addition to mediating vasoconstriction, ET-1 is known to be a potent mitogen, with the ability to induce proliferation in a number of cell types, including vascular smooth muscle cells [8]. It has been shown that the mitogenic actions of ET-1 are mediated by both the ETA and ETB receptors [9]. ETB receptors on endothelial cells mediate vasodilation via increased production of nitric oxide (NO) and prostacyclin [10]. In addition to its pulmonary vasodilation properties, there are data suggesting that the ETB receptor may actually mediate a

vasoconstrictive effect through a population of ETB receptors located on vascular smooth muscle cells [11]. The vasoconstrictive actions of ETB receptors may become more pronounced in the pathologic setting of pulmonary hypertension than in the normal pulmonary vasculature [12].

In humans with pulmonary hypertension, the roles of abnormal endothelin production and receptor-mediated effects have been well demonstrated. Patients with idiopathic pulmonary arterial hypertension (IPAH) demonstrate higher serum levels of ET-1 than control subjects. Lung specimens from patients with IPAH, when compared to those from patients without pulmonary hypertension, exhibit increased ET-1 staining of the muscular pulmonary arteries and increased expression of preproendothelin-1 (PPET-1) in the endothelial cells of the same vessels [13]. Similarly, elevated ET-1 levels have been seen in patients with PAH associated with congenital heart disease [14] and chronic thromboembolic pulmonary hypertension (CTEPH).

Currently Available Endothelin Receptor Antagonists

The discovery, testing, and approval of oral endothelin receptor antagonists (ERA) exemplifies true translational research, that is, insights into the vascular pathobiology of PAH coupled with systematic clinical trials and drug development. This coupling of academia and the pharmaceutical industry led directly to breakthroughs in the treatment of a life-threatening disease, and has led to dramatic improvements in patients' lives and outcomes.

Bosentan

Bosentan is a dual ERA and ERB antagonist that became the first orally active drug for the treatment of PAH when it received Food and Drug Administration (FDA) approval in November 2001. It is indicated for the treatment of WHO group 1 PAH patients in WHO functional class III or IV PAH. The first double-blind, placebo-controlled trial randomized 32 patients with IPAH (84 %) or PAH associated with scleroderma, functional class III, to bosentan or placebo for 12 weeks [15]. The primary endpoint was the placebo-corrected change in 6-min walk distance (6-MWT), with secondary endpoints including change in pulmonary hemodynamics, WHO functional class, Borg dyspnea index, and clinical worsening. The placebo-corrected improvement in 6-MWT was 76 m in favor of the bosentan group. In addition, cardiac index and pulmonary vascular resistance (PVR) were significantly improved with bosentan. There were asymptomatic increases in liver aminotransferases in two patients on bosentan, but these returned to baseline without discontinuing or changing the dose.

The subsequent BREATHE-1 (bosentan randomized trial of endothelin antagonist therapy) trial randomized 213 patients with IPAH (70 %) and pulmonary hypertension associated with connective tissue disease who were WHO functional classes

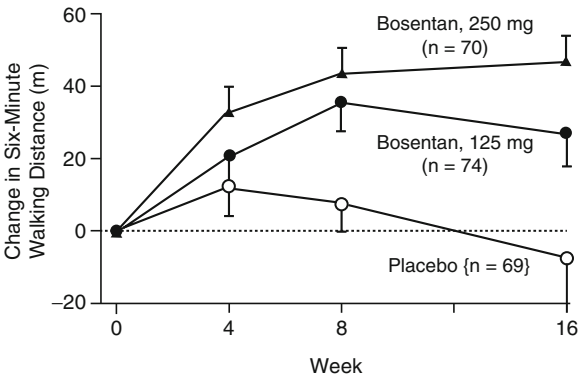


Fig. 14.1 Effect of bosentan on the primary endpoint of change in 6-min walk distance at week 16 from the BREATHE-1 trial. Based on a placebo-corrected improvement in walk distance of 44 m, and its safety profile, bosentan was approved at a dose of 125 mg twice daily (From [16])

III and IV to placebo or bosentan at a dose of 125 or 250 mg twice daily. At 16 weeks, the bosentan group had a placebo-corrected 6MWD improvement of 44 m ($p<0.001$) (Fig. 14.1) [16]. In addition, there were improvements in the Borg dyspnea score and time to clinical worsening in both bosentan groups. Increases in liver aminotransferases greater than eight times upper limit of normal were again noted in the bosentan group and were dose-dependent with two patients in the 125 mg group and five patients in the 250 mg group.

In addition to the above "registration" trials of bosentan, a randomized controlled trial of bosentan in PAH patients less functionally impaired (WHO class II), the EARLY trial, demonstrated a benefit in reducing PVR and preventing clinical worsening at 6 months. No statistically significant effect on 6MWD was seen, although baseline walk distance was greater than 400 m, confirming that this cohort had better baseline exercise capacity [17].

Long-term survival data in patients on bosentan, although uncontrolled, have been published. Of the 169 IPAH patients enrolled in the two pivotal trials of bosentan, estimated survival at 1 year and 2 years was 96 % and 89 % respectively, as compared to the predicted survival of 69 % and 57 % [18] (based on a validated NIH equation calculating predicted survival from baseline hemodynamics). It should be acknowledged that there are no prospective controlled survival data with the newer agents, given obvious ethical concerns about such trials in the era of existing therapy.

Bosentan is primarily metabolized in the liver through the P450 enzyme system. Clinical trials have shown that bosentan can precipitate hepatocellular injury, in particular when given at higher doses. Combined data from multiple trials have shown that there is a greater incidence in hepatic injury in patients treated with bosentan when compared to placebo. Greater than threefold elevations in aminotransferases were seen in 11 % of bosentan-treated patients ($n=658$) compared with 2 % of patients treated with placebo ($n=280$).

In the BREATHE-1 study, increases in hepatic aminotransferases occurred in 10 % of the patients and were found to be dose-dependent (more frequent in the

250 mg group), and reversible with dose reductions or upon stopping the drug. Based on these findings, the recommended dose of bosentan is 125 mg twice daily. Patients on bosentan must undergo baseline monitoring of liver function tests prior to initiation of the drug, and monthly thereafter.

Bosentan in Other Types of Pulmonary Hypertension

The initial bosentan trials only included adult patients with IPAH and associated PAH, predominantly scleroderma or connective tissue-related PAH. Data regarding the use of bosentan in other classes of PAH are limited. BREATHE-4 was a small, uncontrolled, prospective study of 16 patients with class III and IV HIV-associated PAH. The study found that HIV-associated PAH patients treated with bosentan had similar safety and efficacy profiles to prior groups studied [19]. At 16 weeks there were significant improvements in 6MWD, echocardiographic parameters, and quality of life scores. However, there was no comparison placebo arm. There was also an improvement in functional class, with 14 out of the 16 patients improving at least one class when compared to baseline. Treatment with bosentan did not have a negative impact on control of HIV infection. In this small study, bosentan had similar hepatic tolerability to that found in other patients with PAH, despite several patients being co-infected with either hepatitis B or C virus. In patients with hepatitis co-infection, bosentan should be used with caution and frequent monitoring of liver function tests.

BREATHE-5 was a randomized, placebo-controlled trial that evaluated the effect of bosentan in patients with Eisenmenger's syndrome due to congenital heart disease and functional class III PAH [20]. Fifty-four patients were randomized in a 2:1 fashion to bosentan ($n=37$) or placebo ($n=17$) for 16 weeks. Bosentan treatment did not reduce systemic arterial blood oxygen saturation, and showed significant improvement in hemodynamics (PVR, mPAP) and exercise capacity, with a treatment effect of +53 m in 6MWD. An open-label extension of this study revealed improvement in functional class in 24 out of the 37 patients. A subgroup analysis comparing atrial septal defect to ventricular septal defect patients receiving bosentan did not show any significant difference between the two groups [21]. This suggests the location of septal defects is not an important determinant of treatment response with bosentan.

The Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension (BENEFiT) trial investigated bosentan use in CTEPH [22]. One hundred and fifty-seven patients with CTEPH, who had either inoperable disease or persistent pulmonary hypertension 6 months after pulmonary endarterectomy, were enrolled. A statistically significant treatment effect of −24.1 % reduction in PVR was demonstrated in patients treated with bosentan over placebo. There was an improvement in 6MWD, but it did not reach statistical significance.

Ambrisentan

Ambrisentan is a specific ETA receptor antagonist approved for PAH, functional classes II and III at doses of 5 or 10 mg once daily. Following a Phase 2, dosing study showing improvement in pulmonary hemodynamics [23], two randomized controlled trials, ARIES 1 and ARIES 2 (ARIES 1: 5 mg, 10 mg, placebo; ARIES 2: 2.5 mg, 5 mg, placebo) were conducted, enrolling a total of 394 patients [24]. Both trials demonstrated improvement in the primary endpoint of placebo-corrected 6MWD (Fig. 14.2). In ARIES-2, there was a significant improvement in time to clinical worsening in the treatment group as compared with placebo. There was a trend toward improvement in time to clinical worsening in the ARIES-1 study, but it was not statistically significant ($p = 0.307$). World Health Organization

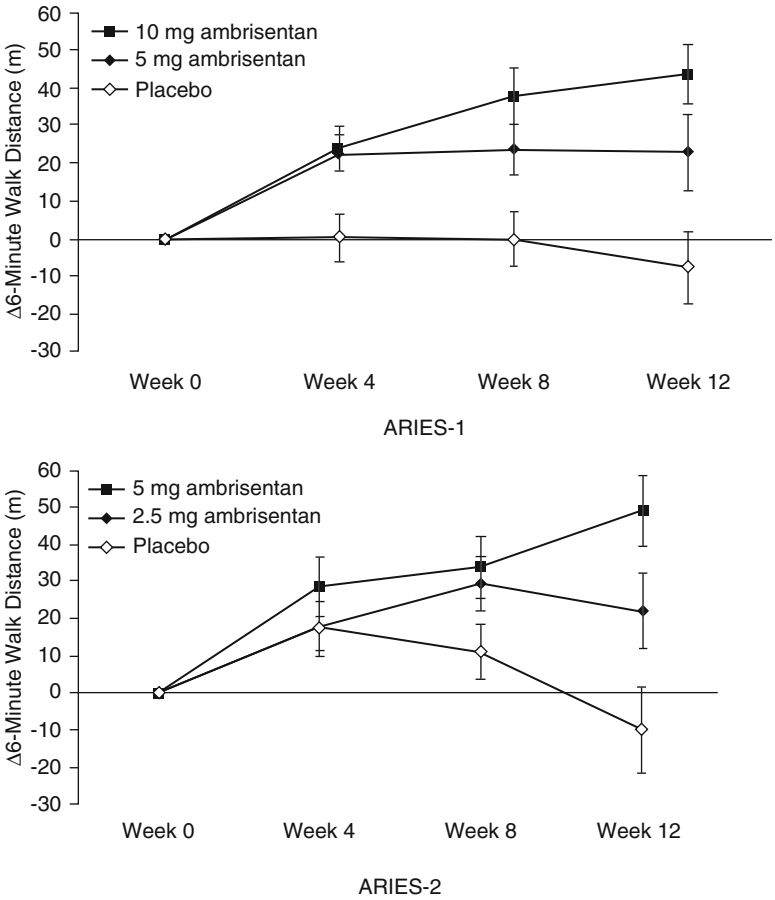


Fig. 14.2 Effect of ambrisentan on the primary endpoint of change in 6-min walk distance at week 12, from the ARIES-1 and ARIES-2 trials. Based on this finding, ambrisentan was approved at doses of 5 mg daily and 10 mg daily (From [24])

(WHO) functional class improvement was significant in ARIES-1 and there was trend toward improvement in ARIES-2 but did not reach statistical significance ($p = 0.117$). Two hundred and ninety-eight patients were enrolled and followed in a long-term extension study over 48 weeks. Eighteen patients required additional therapies (prostanoids or phosphodiesterase type-5 [PDE-5] inhibitors). Of the 280 patients continued on ambrisentan monotherapy, the improvement in 6MWD at 12 weeks was 40 m and maintained at 39 m. Although there were no patients with elevations in serum aminotransferases >3 times upper limit of normal while on ambrisentan, in the trials, long-term follow-up has revealed cases of transaminase elevations which resolve upon discontinuation of ambrisentan. However, because post-marketing surveillance suggested a minimal risk of drug-induced liver toxicity, the FDA removed the black box warning and requirement for monthly liver function monitoring. However, regular monitoring of pregnancy tests and hemoglobin is still required.

Macitentan

Macitentan is a novel dual ERA that was developed by modifying the chemical structure of bosentan to produce a drug with high oral efficacy and lipophilicity. This led to discovery of several alkyl sulfamide-substituted pyrimidines, including macitentan. Chemically, macitentan is *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N′*-propylsulfamide [25].

Compared with bosentan and ambrisentan, macitentan has a higher pKa and distribution coefficient, resulting in a higher percentage of nonionized drug at physiologic pH and favoring distribution across the phospholipid bilayer of the cell membrane. Compared to bosentan, macitentan also has improved receptor association and dissociation kinetics with more sustained receptor binding [26]. In human pulmonary artery smooth muscle cells, this leads to insurmountable antagonism and suggests that macitentan may have the ability to block endothelin more effectively in the setting of variable endothelin levels.

Macitentan: Initial Phase 1 and 2 Clinical Trials

Macitentan was first studied in healthy subjects in single dose followed by ascending multiple dose studies of 1–30 mg of macitentan versus placebo [27]. In these studies, macitentan was well tolerated and pharmacokinetics were supportive of once daily dosing with a maximal effect on endothelin levels at a dose of 10 mg. The half-life of macitentan was 14–18 h, while the half-life of ACT-132577, an active but less potent metabolite, was approximately 48 h. Drug elimination and formation of the active metabolite is catalyzed by cytochrome (CYP) P450, predominantly CYP3A4 and CYP2C19.

Macitentan: Phase 3 Clinical Trial

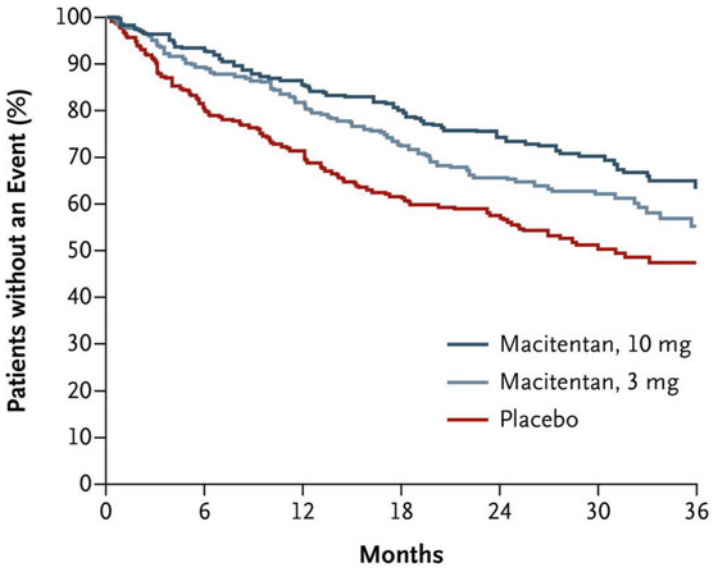
The landmark Phase 3 clinical trial that led to approval of macitentan in the U.S. and several other countries was the SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcomes) trial [28]. The study was designed as an event-driven morbidity and mortality trial. In this study, 742 patients with symptomatic PAH (52 % FC II, 46 % FC III and 2 % FC IV) were randomized 1:1:1 to receive placebo ($n=250$), macitentan 3 mg ($n=250$), or macitentan 10 mg ($n=242$) and were followed for a median duration of 115 weeks. The study cohort included patients with idiopathic and heritable PAH (57 %), PAH associated with connective tissue disease (31 %), PAH associated with congenital heart disease (8 %), and PAH associated with HIV or drug/toxin exposure (4 %). Sixty-four percent of patients were on stable background PAH therapy with phosphodiesterase inhibitors or oral or inhaled prostanoids which they were allowed to continue throughout the study.

The primary endpoint was time from initiation of treatment to the first occurrence of a morbidity event related to PAH or death from any cause in an intention-to-treat analysis. The components of the morbidity/mortality event endpoint included death, atrial septostomy, lung transplantation, initiation of intravenous or subcutaneous prostanoids, or a composite endpoint for worsening of PAH.

The primary endpoint occurred in 46.4 ($n=116$), 38 ($n=95$), and 31.4 % ($n=76$) of patients treated with placebo, macitentan 3 mg and macitentan 10 mg, respectively, with a hazard ratio of 0.70 (97.5 % CI, 0.52–0.96; $p=0.01$) for macitentan 3 mg versus placebo and a hazard ratio of 0.55 (97.5 % CI 0.39–0.76; $p<0.001$) for macitentan 10 mg versus placebo (Fig. 14.3). Worsening of PAH was the most frequent first event, which is not unexpected since worsening of PAH often precedes other components of the endpoint, such as initiation of prostanoids or mortality.

A prespecified secondary endpoint, death or hospitalization due to PAH, occurred in 33.6 % of the placebo group, 26 % of the macitentan 3 mg group and 20.7 % of the macitentan 10 mg group with a hazard ratio of 0.67 (97.5 % CI, 0.46–0.97, $p=0.01$) for macitentan 3 mg versus placebo and a hazard ratio of 0.50 (97.5 % CI 0.34–0.75, $p<0.001$) for macitentan 10 mg versus placebo (Fig. 14.3). Hospitalization accounted for the majority of these events, and there was no statistically significant difference in mortality between the groups. The study, however, was not designed or powered to show an effect on the endpoint of mortality alone.

The benefit of macitentan was observed irrespective of background therapy for PAH; macitentan 10 mg reduced the risk of the primary endpoint by 38 % (95 % CI 11–57 %) in the presence of background PAH therapy and 55 % (95 % CI 28–72 %) in the absence of PAH background therapy. Macitentan also demonstrated an improvement in secondary endpoints, including functional class and exercise capacity. In a subset of 145 patients who had right heart catheterizations and pulmonary hemodynamics reported at baseline and month 6, patients in both macitentan groups also had significant decreases in PVR (66.4 % [95 % CI 56.6–77.8 %] and 61.5 %



No. at Risk							
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Fig. 14.3 Effects of macitentan compared to placebo on time to first morbidity/mortality event. The hazard ratio for macitentan 10 mg daily compared to placebo was 0.55 (relative risk reduction of 45 % over the course of the study). Based on this finding, macitentan was approved at 10 mg daily (From [28])

[95 % CI 62.4–81.4 %] of placebo-corrected change from baseline for 3 mg and 10 mg macitentan, respectively) and an increase in cardiac index (0.69 L/min/m^2 [95 % CI 0.40–0.97] and 0.63 L/min/m^2 [95 % CI 0.28–0.97] placebo-corrected change from baseline for 3 mg and 10 mg macitentan, respectively).

SERAPHIN was the first event-driven study ever done in PAH. Compared to other clinical trials that led to drug approval for ambrisentan and bosentan in which patients were only exposed to therapy for 12–16 weeks [15, 16, 24], the treated patients in SERAPHIN had a median drug exposure of 115 weeks. Additionally, compared to other studies that have predominantly evaluated PAH monotherapy versus placebo, this study also included patients on background PAH therapy and demonstrated a beneficial effect of macitentan as monotherapy or in combination with other PAH medications. It is also important to note that even in patients on background PAH therapy, there was a significant incidence of morbidity/mortality over the course of the study, which was decreased with macitentan.

In SERAPHIN, the occurrence of aminotransferase elevation or edema and the number of people discontinuing treatment due to adverse effects were similar in

placebo and active treatment groups. There was a small, dose-related decrease in hemoglobin from macitentan. Based on the results of SERAPHIN, macitentan (Opsumit, Actelion Pharmaceuticals) was approved by the United States FDA in October 2013 for the treatment of patients with Group 1 PAH and functional class II–IV symptoms at a recommended dose of 10 mg daily. It became commercially available for use in the United States in November 2013. Similar to ambrisentan, there is no required monthly liver function test monitoring for macitentan.

Comparing ERAs to Other PAH Therapy

ERAs have rarely been compared to other PAH therapies in head-to-head trials. The Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) trial directly compared bosentan to sildenafil. Twenty-six patients with class III PAH (IPAH and associated with connective tissue disease) were randomized to receive either sildenafil (50 mg b.i.d. for 4 weeks followed by 50 mg t.i.d.) or bosentan (62.5 mg b.i.d. for 4 weeks followed by 125 mg b.i.d.) as initial PAH monotherapy [29]. After 16 weeks, there was not a significant difference between the two groups in 6MWD, right ventricular mass, cardiac function, brain natriuretic peptide, or Borg dyspnea score.

A retrospective analysis compared 139 class III IPAH patients initially treated with bosentan monotherapy, to a historical cohort of 346 class III IPAH patients who were initially treated with intravenous epoprostenol [30]. Survival estimates up to 36 months were not significantly different in those initially treated with bosentan compared with those initially treated with epoprostenol. This suggests that initial treatment with oral bosentan in class III idiopathic PAH patients, followed by or with the addition of other treatment if necessary, does not adversely affect the long-term outcome compared with initial intravenous epoprostenol therapy. A pilot study was then conducted to see if PAH patients stable on prostacyclin therapy could be transitioned to oral bosentan therapy [31]. This was an open-label trial of 22 PAH patients who were clinically stable on intravenous epoprostenol or subcutaneous treprostinil for at least 3 months. The patients were observed closely while bosentan was added and prostracyclin therapy was titrated down. Ten out of the 22 patients were transitioned off prostacyclin therapy after a mean duration of 6 months. Seven out of those ten patients remained stable off of prostacyclin, for a mean duration of 18 months. Three patients who were titrated off required re-initiation of prostacyclin therapy given clinical deterioration, with two of these resulting in death. Of the 12 patients who did not tolerate off-titration of prostacyclin, 2 subsequently died. Those who transitioned successfully were on a lower baseline prostacyclin dose and had lower mPAPs than those who failed.

The guidelines, as developed at the 5th World Symposium on PH, give all three available ERAs a Grade 1 recommendation for PAH patients who are Functional Class II or III, and Grade 2 recommendation for PAH patients who are Functional Class IV [32].

Combination Therapy with ERAs

ERAs are commonly used in combination with other PAH therapies. The current World Symposium guidelines support this approach, based on emerging data [32]. This combination approach has generally been studied in a sequential, add-on fashion, with ERAs often being the first-line agents.

The effect of bosentan as add-on therapy to prostacyclins was studied in a prospective trial of 20 patients with IPAH who were either on inhaled iloprost ($n=9$) or oral beraprost ($n=11$) [33]. Combination therapy was tolerated by all patients. After 3 months of combination therapy, exercise tolerance increased by 58 m, and maximal oxygen consumption (measured by cardiopulmonary stress test) increased from 11 to 13.8 ml/kg/min, when compared to baseline. Another small prospective study added bosentan 62.5 mg twice daily to eight IPAH patients who were already on high-dose intravenous epoprostenol [34]. The addition of bosentan was well tolerated and seven out of eight patients had a reduction in the epoprostenol dose from an average of 99.6 ng/kg/min down to 82.8 ng/kg/min. Treatment effects were maintained for a total of 1 year and only two patients had progression of disease. A retrospective study on PAH patients receiving subcutaneous treprostinil found that 19 out of 38 patients had received add-on therapy with bosentan because they remained functional class III on treprostinil monotherapy. The patients who received add-on bosentan therapy showed significant improvement in pulmonary pressures, 6MWT distance, and Borg dyspnea score [35].

The BREATHE-2 trial was a double-blind, placebo-controlled, prospective study which looked at combination upfront therapy with IV epoprostenol and bosentan [36]. Thirty-three patients with class III or IV PAH were randomized in a 2:1 ratio to receive bosentan 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily or placebo, 2 days after starting IV epoprostenol. At 16 weeks, both groups had a decrease in the primary outcome of total pulmonary resistance (TPR). There was a trend toward a greater decrease from baseline TPR in the bosentan/epoprostenol group, which was not statistically significant.

Adverse Effects Associated with ERAs

Several potentially serious adverse reactions can occur with the use of ERAs. All ERAs presently available for the treatment of PAH are teratogenic and woman of child-bearing potential need to be counseled about the potential of severe birth defects to their child if they become pregnant while taking these medications. Women who are sexually active should use two reliable forms of birth control. Serum pregnancy test is required prior to starting therapy and monthly thereafter.

Elevation of liver transaminases can occur in patients taking ERAs, particularly with bosentan. As a result, the FDA has mandated monthly liver function testing (LFT) for all patients who are treated with bosentan as long as they are receiving

drug. Extended LFT monitoring after drug discontinuation is not needed. Drug should be stopped if there is an elevation of AST or ALT greater than five times the upper limit of normal or elevation in total bilirubin greater than two times the upper limit of normal. Bosentan therapy can be continued at a reduced dose if AST or ALT rises between three and five times the upper limit of normal, but LFTs should be monitored more frequently thereafter. Although elevation of transaminases is seen less frequently with the other ERAs and monitoring of LFTs is not mandatory, it is recommended that LFTs be measured prior to starting therapy with ambrisentan or macitentan and quarterly thereafter or at the discretion of the practitioner.

Other common adverse effects associated with ERA use include drug interactions, peripheral edema, and low-grade anemia. The ERAs are metabolized primarily in the liver by cytochrome p450 isoenzymes CYP2C9, CYP3A4 and to a lesser extent CYP2C19. Use of the ERAs in conjunction with other medications that induce or inhibit this pathway have potential to cause significant interactions. Drugs that inhibit these isoenzymes such as ketoconazole, cyclosporine A or ritonavir, increase plasma levels of ERAs and should be avoided or used with caution. The incidence of LFT abnormalities is also increased when bosentan is taken with glyburide. At the same time, bosentan has been shown to decrease plasma levels of warfarin and oral hypoglycemic agents and the dose of these drugs may need to be adjusted if given with bosentan. Peripheral edema is usually controlled with low-dose diuretics, but in some patients may be unmanageable and necessitate switching to another drug. Patients should always be evaluated for other causes of increasing edema such as heart and renal failure. The anemia that has been associated with ERA use is usually mild with the average decrease in hemoglobin about 1 g/dl, but decreases greater than 15 % from baseline have also been reported. The decrease in hemoglobin usually occurs within the first month and remains fairly stable thereafter. Blood counts should be measured prior to the start of ERA therapy and a month later and then at the discretion of the practitioner.

Due to the number of potential adverse events associated with the use of ERAs, these drugs are only available through specialty pharmacies and patients are required to sign a consent form acknowledging potential adverse effects prior to starting therapy.

Summary

The treatment of PAH remains complex with an increasing number of therapeutic options. Treatment should be individualized and guided by the patient's clinical status and hemodynamic testing. There are now evidence-based treatment algorithms for the initial treatment of PAH [32, 37]. Expert guidelines recommend the use of ERA in PAH patients who are functional class II and III. In patients treated with bosentan, monthly liver function tests should be monitored. If after 2–3 months of therapy there is not an improvement in functional class or exercise capacity, or if there is clinical decline, addition of prostanoids or phosphodiesterase inhibitors should be considered.

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