Long-Term Ambrisentan Therapy for the Treatment of Pulmonary Arterial Hypertension

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Objectives

This study evaluated the safety and efficacy of ambrisentan for a period of 2 years in patients with pulmonary arterial hypertension (PAH).

Background

Ambrisentan is an oral, once-daily endothelin receptor antagonist that is selective for the endothelin type A receptor. The ARIES-1 (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies) and ARIES-2 trials were the pivotal 12-week, placebo-controlled studies that led to the regulatory approval of ambrisentan (5 and 10 mg) for the treatment of PAH.

Methods

In the ARIES-1 and -2 studies, and the subsequent long-term extension protocol, the ARIES-E study, 383 patients received ambrisentan (2.5, 5, or 10 mg). Efficacy and safety assessments are presented from the time of the first dose of ambrisentan for all patients with post-baseline data.

Results

After 2 years of ambrisentan exposure, the mean change from baseline in 6-min walk distance was improved for the 5-mg (23 m; 95% confidence interval: 9 to 38 m) and 10-mg (28 m; 95% confidence interval: 11 to 45 m) groups. Estimates of survival and freedom from clinical worsening for the combined dose group were 94% and 83%, respectively, at 1 year and 88% and 72%, respectively, at 2 years. The annualized risk of aminotransferase abnormalities exceeding the upper limit of normal was 2% per year; most of these events were mild and did not lead to discontinuation of drug.

Conclusions

Two years of ambrisentan treatment was associated with sustained improvements in exercise capacity and a low risk of clinical worsening and death in patients with PAH. Ambrisentan was generally well tolerated and had a low risk of aminotransferase abnormalities over the 2-year study period. (A Long Term Study of Ambrisentan in Pulmonary Arterial Hypertension Subjects Having Completed AMB-320 or AMB-321; NCT00578786) (J Am Coll Cardiol 2009;54:1971–81) © 2009 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a disease of the pulmonary circulation characterized by a progressive elevation in pulmonary vascular resistance that leads to right ventricular failure and premature death. Although the number of approved therapies for PAH has grown in the past 10 years, the disease remains rapidly progressive with a poor prognosis and approximately 50% mortality during the first 5 years after diagnosis (1–3).

Three signaling pathways involved in the pathogenesis of PAH have been targeted for therapeutic intervention: the relationships with Gilead Sciences, Inc., the sponsor of the study. These relationships include consultancy, membership on steering committees, and support for work as investigators. The database and all statistical outputs were retained by the sponsor, Gilead Sciences, Inc. One statistician involved in the analysis (Mr. Despain) is an employee of the sponsor; however, these data were also reviewed by an independent statistician not affiliated with the sponsor (Dr. Roecker). Gerald Simonneau, MD, served as Guest Editor for this article.

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prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway (4). Prostacyclin analogs mimic the effects of prostacyclin, an endogenous prostaglandin produced by the vascular endothelium, to stimulate vasodilation of the pulmonary arterial bed and inhibit platelet aggregation (5). Phosphodiesterase type 5 inhibitors act to increase cytoplasmic cyclic guanosine monophosphate concentrations (the downstream product of nitric oxide signaling) and thus enhance nitric oxide–mediated vasodilation of the vasculature (6). Endothelin receptor antagonists (ERAs) act to diminish the downstream effects of endothelin (ET)-1, the primary member of a family of potent vasoconstrictor peptides known to play an essential role in cardiovascular physiology and thought to play a critical role in the pathogenesis and progression of PAH (7–10). Two receptor subtypes, endothelin receptor type A (ET\textsubscript{A}) and endothelin receptor type B (ET\textsubscript{B}), mediate the effects of ET-1. In humans, the ET\textsubscript{A} receptor is preferentially expressed in vascular smooth muscle cells and fibroblasts, where it promotes the vasoconstrictive and mitogenic effects of ET-1 (11,12). In contrast, ET\textsubscript{B} receptors are found primarily in the vascular endothelium, and activation of these receptors results in vasodilation via the production of nitric oxide and prostacyclin (13,14). The ET\textsubscript{B} receptors also mediate the clearance of circulating ET-1 in the lungs, kidney, and liver (15). Thus, the ET\textsubscript{A} receptor represents a logical pharmacologic target.

Ambrisentan is an orally active, once-daily ET\textsubscript{A}-receptor selective ERA that is currently approved (5 and 10 mg) in the U.S., European Union, Australia, Canada, Norway, Iceland, and Israel for the treatment of PAH. In 2 pivotal, 12-week, placebo-controlled studies (ARIES-1 [Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies] and ARIES-2), ambrisentan improved exercise capacity along with other clinical indications of PAH disease severity, including clinical worsening (16). The ARIES-E study was the long-term extension study for patients in the ARIES-1 and -2 studies. The objective of the ARIES-E study was to collect long-term safety and efficacy data for PAH patients receiving ambrisentan.

Methods

Clinical studies. An integrated analysis of all patients who received at least 1 dose of ambrisentan in the ARIES-1, -2, or -E studies is presented. In the ARIES-1 study, 202 patients were randomized (1:1:1) to placebo, 5 mg ambrisentan, or 10 mg ambrisentan, whereas in the ARIES-2 study, 192 patients were randomized (1:1:1) to placebo, 2.5 mg ambrisentan, or 5 mg ambrisentan. The ARIES-1 and -2 patient populations have been described previously (16).

In brief, these studies included patients with idiopathic PAH or PAH associated with connective tissue disease, human immunodeficiency virus infection, or anorexigen use. At the time of screening, patients could not be receiving ERA, phosphodiesterase type 5 inhibitor, or prostacyclin analog therapy and were required to have serum aminotransferase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) concentrations <1.5× the upper limit of normal (ULN). Patients who completed the ARIES-1 or -2 study were eligible to receive long-term ambrisentan treatment in the ARIES-E study. Patients who received ambrisentan during the 12-week studies remained on their current dose at enrollment into the ARIES-E study, whereas patients who received placebo were randomized to ambrisentan treatment (ARIES-1: 5 or 10 mg once daily; ARIES-2: 2.5 or 5 mg once daily).

The first 24 weeks of the ARIES-E study was a blinded, fixed-dose period; however, a single, blinded dose reduction was permitted during this period in the event of study drug intolerance. After 24 weeks, the randomized treatment assignment remained blinded but dose adjustments were permitted per investigator discretion (available doses: 1, 2.5, 5, and 10 mg).

Patients were assessed for safety and efficacy every 4 weeks during the 12-week placebo-controlled ARIES-1 and ARIES-2 studies. In the ARIES-E study, safety and efficacy were assessed at weeks 4, 12, 16, 24, 36, and 48, and at 24-week intervals thereafter. Safety assessments included monitoring of adverse events, clinical laboratory tests (every 4 weeks), vital signs, and physical examination. Female patients of child-bearing potential underwent monthly urine pregnancy testing and were instructed to avoid pregnancy by using a double-barrier method of contraception.

Efficacy assessments included 6-min walk distance (6MWD), Borg dyspnea index, World Health Organization (WHO) functional class, long-term survival, and time to clinical worsening. Time to clinical worsening was defined as the time from first dose of ambrisentan to first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, addition of prostacyclin analog therapy, study withdrawal because of the addition of other PAH drugs, or study withdrawal because of early escape. As described previously, patients who met 2 or more predefined criteria during the ARIES-1 or -2 study were eligible to request early escape (after a minimum of 4 weeks of blinded treatment) (16). Patients receiving placebo who met early escape criteria were eligible to enroll in the ARIES-E study.

Data analysis. For all efficacy and safety assessments, baseline was defined as the time of randomization to active study drug. The analysis population included all patients who received at
least 1 dose of ambrisentan in the ARIES-1, -2, or -E study. For 6MWD, Borg dyspnea index, and WHO functional class, the primary analysis was conducted using a last observation carried forward imputation for missing data and included all patients with post-baseline data. An analysis of observed data with no imputation for missing data (observed case) is also presented as a sensitivity analysis. Sample size was based on the number of subjects that participated in the ARIES-1 and -2 studies; therefore, there were no a priori estimates of power for the various long-term assessments. Data are presented by randomized ambrisentan treatment group, and descriptive statistics are presented without formal hypothesis testing.

Because of the visit schedule in the ARIES-E study, safety and efficacy data were assessed after the first year of treatment at different intervals of ambrisentan exposure for patients who initially received ambrisentan or placebo in the ARIES-1 or -2 studies. To account for these differences, analysis of 6MWD, Borg dyspnea index, and WHO functional class included the following time points: baseline (immediately before first dose of ambrisentan), 12 weeks, 24 weeks, 1 year (48 weeks), 1.5 years (72 or 84 weeks), and 2 years (96 or 108 weeks). Safety data and Kaplan-Meier estimates of long-term survival, time to ALT/AST >3×ULN, and time to study discontinuation because of adverse events are presented through 1 year (52 weeks) and 2 years (104 weeks) of treatment. For Kaplan-Meier analyses, patients who discontinued the study without experiencing an event were censored at the time of discontinuation.

This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients.

Results

Baseline characteristics. Baseline characteristics were similar across the 3 dose groups (Table 1). Overall, patients were mostly Caucasian (77%) and female (79%), with idiopathic PAH (63%) and WHO class II (43%) or III (46%) symptoms. The mean baseline 6MWD was 347 ± 85 m, and the mean Borg dyspnea index was 3.9 ± 2.4.

Patient disposition. A total of 383 patients received at least 1 dose of ambrisentan (2.5 mg [n = 96], 5 mg [n = 190], or 10 mg [n = 97]) in the ARIES-1, -2, or -E studies (Fig. 1). This population included 350 patients who completed the placebo-controlled period and enrolled in the ARIES-E study, 11 placebo patients who discontinued 1 of the 12-week studies because of early escape and subse-

<table>
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<th>Table 1 Baseline Characteristics</th>
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<th>Characteristic</th>
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<th>10 mg (n = 97)</th>
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<td>154 (81)</td>
<td>79 (81)</td>
<td>302 (79)</td>
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<td>52 ± 15</td>
<td>51 ± 14</td>
<td>49 ± 17</td>
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<td>2 (2)</td>
<td>11 (3)</td>
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<td>2 (2)</td>
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<td>348 ± 87</td>
<td>342 ± 81</td>
<td>347 ± 85</td>
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<td>Borg dyspnea index</td>
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<td>3.8 ± 2.3</td>
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<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>50 ± 14</td>
<td>48 ± 14</td>
<td>50 ± 15</td>
<td>49 ± 14</td>
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<td>Cardiac index, l/min/m²</td>
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<td>2.5 ± 0.8</td>
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<td>2.5 ± 0.8</td>
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<td>Pulmonary vascular resistance, mm Hg/l/min/m²</td>
<td>10.4 ± 5.3</td>
<td>11.2 ± 7.3</td>
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<td>11.0 ± 6.5</td>
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<td>Right atrial pressure, mm Hg</td>
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<td>8.0 ± 4.8</td>
<td>8.8 ± 5.3</td>
<td>8.2 ± 5.1</td>
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Values are mean ± SD or n (%). Baseline is defined as the time of first dose of ambrisentan. All hemodynamic data are historical. All data are presented by randomized ambrisentan dose. HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; WHO = World Health Organization.
quently enrolled in the ARIES-E study, and 22 patients who received ambrisentan in 1 of the 12-week studies but did not enroll in the ARIES-E study.

At 1 year, 315 patients remained on ambrisentan treatment, with 91% of these patients receiving ambrisentan monotherapy. At 2 years (Fig. 1), 261 patients were on ambrisentan treatment, with 82% of these patients receiving ambrisentan monotherapy, 10% receiving ambrisentan/sildenafil therapy, 5% receiving ambrisentan/prostacyclin analog therapy, and 3% receiving ambrisentan/sildenafil/prostacyclin analog therapy. An additional 22 patients discontinued from the study and transitioned to commercial drug before receiving 104 weeks of ambrisentan therapy (study drug exposure range 75 to 102 weeks). Of these 22 patients, 19 had 2-year data collected for 6MWD, Borg dyspnea index, and WHO functional class, whereas the remaining 3 provided data collected through 1.5 years of treatment.

Over the 2-year period, 42 patients died and 22 patients discontinued because of adverse events. The percentages of patients who died during the 2-year period were 14%, 11%, and 8% for the 2.5-, 5-, and 10-mg groups, respectively. In general, nearly all dose adjustments during the 2-year treatment period were up-titrations in the 2.5-mg (28 of 28) and 5-mg (50 of 54) groups; only 3 dose reductions were observed in the 10-mg group.

**Exercise capacity.** Figure 2A shows the change from baseline in 6MWD using the last observation carried forward for missing data. After 1 year of ambrisentan treatment, improvements in 6MWD were observed for all dose groups, with a change from baseline of $+25$ m (95% confidence interval [CI]: 5 to 45 m) for the 2.5-mg group, $+28$ m (95% CI: 14 to 42 m) for the 5-mg group, and $+37$ m (95% CI: 22 to 52 m) for the 10-mg group. After 2 years of ambrisentan treatment, improvements compared with baseline in 6MWD were maintained for the 5-mg ($+23$ m; 95% CI: 9 to 38 m) and 10-mg ($+28$ m; 95% CI: 11 to 45 m) groups, whereas improvements in 6MWD did not seem to be sustained in the 2.5-mg group at 2 years ($+7$ m; 95% CI: $-13$ to 27 m). Similar results were observed when the data were analyzed with no imputation for missing data (oberved case) (Fig. 2B). At 2 years, the mean change from baseline was $+21$ m (95% CI: $-2$ to 45 m) for the 2.5-mg
group, +47 m (95% CI: 31 to 63 m) for the 5-mg group, and +38 m (95% CI: 19 to 57 m) for the 10-mg group.

**Additional clinical end points.** After 1 year of treatment, sustained improvements in Borg dyspnea index were observed for the 5-mg (−0.59; 95% CI: −0.94 to −0.23) and 10-mg (−0.51; 95% CI: −1.00 to −0.03) groups compared with baseline (last observation carried forward) (Fig. 3); no improvement in Borg dyspnea index was observed in the 2.5-mg group (0.08; 95% CI: 0.55 to 0.38). This trend continued through 2 years of treatment, with a mean change from baseline of −0.33 (95% CI: −0.68 to 0.03) for the 5-mg group, −0.60 (95% CI: −1.08 to −0.11) for the 10-mg group, and +0.23 (95% CI: −0.31 to 0.76) for the 2.5-mg group. Similar results were observed at 2 years when the data were analyzed with no imputation for missing data: 2.5-mg group (+0.28; 95% CI: −0.35 to 0.90), 5-mg group (−0.53; 95% CI: −0.98 to −0.08), and 10-mg group (−0.95; 95% CI: −1.45 to −0.45). As shown in Table 2, WHO functional class was either improved or maintained through 2 years for the majority of patients in each dose group (range 79% to 89%). Similar trends were observed when the data were analyzed with no imputation for missing data (range 86% to 90%; data not shown).

**Long-term survival and clinical worsening.** Overall, 42 patients died during the 2-year treatment period (Table 3). Most patient deaths were classified by the investigators as related to the underlying PAH; the most frequent adverse events with an outcome of death were right ventricular failure (3.1%), worsening pulmonary hypertension...
(1.6%), and acute respiratory failure (1.0%). The Kaplan-Meier survival estimate for the overall population was 94% (95% CI: 91% to 96%) at 1 year and 88% (95% CI: 83% to 91%) at 2 years (Fig. 4). Similar results were observed within each dose group at 1 year (range 93% to 97%) and 2 years (range 85% to 91%) of treatment (Fig. 4). For the idiopathic PAH patient subgroup (n = 241), survival was 96% (95% CI: 92% to 98%) at 1 year and 89% (95% CI: 84% to 93%) at 2 years, whereas the estimated survival for this patient population based on the National Institutes of Health Registry formula was 72% at 1 year and 61% at 2 years. Survival was similar in patients with PAH associated with connective tissue disease at 1 year (91%; 95% CI: 84% to 95%) and 2 years (83%; 95% CI: 75% to 89%) compared with patients with idiopathic PAH.

After 1 year of treatment, 83% (95% CI: 79% to 87%) of the overall population was free from clinical worsening (Kaplan-Meier estimate), whereas 72% (95% CI: 67% to 76%) of patients were clinical worsening event–free after 2 years of treatment (Fig. 5). As with long-term survival, similar results were observed by dose group after 1 year (range 81% to 84%) and 2 years (range 70% to 73%) of treatment (Fig. 5). During the 2-year treatment period, hospitalization for PAH was the most common clinical worsening event in all treatment groups (Table 3). A post-hoc analysis of time to clinical worsening by prior study (i.e., the ARIES-1 or -2 studies) showed similar 2-year event-free rates: ARIES-1, 5 mg (70% [95% CI: 59% to 78%]); ARIES-1, 10 mg (72% [95% CI: 62% to 80%]); ARIES-2, 2.5 mg (70% [95% CI: 59% to 78%]); and ARIES-2, 5 mg (76% [95% CI: 65% to 84%]).

Safety. The most common adverse events during the 2-year treatment period were peripheral edema, headache, upper respiratory tract infection, and dizziness. Most peripheral edema was mild (21%) or moderate (16%); however, 5 (1.3%) patients experienced severe peripheral edema during the 2-year observation period (1 patient in the 2.5-mg group, 2 patients in the 5-mg group, and 2 patients in the 10-mg group). One patient discontinued ambrisentan treatment during the 2-year treatment period because of peripheral edema. The most common adverse events that led to discontinuation of ambrisentan or death during the 2-year treatment period were right ventricular failure (3.9%), pul-
Pulmonary hypertension (3.7%), acute respiratory failure (1.0%), and cardiac arrest (0.8%). In general, similar results were observed in each of the dose groups, although there seemed to be a greater percentage of patients who discontinued because of worsening pulmonary hypertension in the 2.5-mg group (7.3%) as compared with either the 5-mg (2.1%) or 10-mg (3.1%) groups (Table 4).

For the overall study population, the estimated risk of developing serum aminotransferase abnormalities (ALT/AST) was 1.8% (95% CI: 0.8% to 3.9%) during the first year of treatment and 3.9% (95% CI: 2.2% to 6.8%) during the cumulative 2-year treatment period (Fig. 6), for an annualized risk of approximately 2%. Twelve patients experienced ALT/AST >3× ULN during the 2-year period. For these 12 patients, the maximum ALT/AST was >3× and ≤5× ULN for 10 patients and >8× ULN for 2 patients. None of the 12 patients had concomitant bilirubin >2× ULN, and only 2 patients discontinued ambrisentan treatment because of aminotransferase abnormalities. A reduction in mean hemoglobin concentration of −0.9 g/dl was observed at week 4, and this reduction was largely maintained through 108 weeks of ambrisentan treatment (−1.2 g/dl). Reductions in mean hemoglobin at 2 years did not seem to be dose dependent (2.5 mg: −1.1 g/dl, 5 mg: −1.1 g/dl, 10 mg: −1.2 g/dl). Minimal changes in international normalized ratio (mean ± SD) were observed over the course of the 2-year study period (baseline: 2.13 ± 1.37, week 108: 2.15 ± 1.08). There were no apparent effects of ambrisentan on warfarin dose or dosing interval (data not shown).

Table 3 Clinical Worsening: Cumulative Incidence of Events Through 1 and 2 Years of Treatment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>2.5 mg (n = 96)</th>
<th>5 mg (n = 190)</th>
<th>10 mg (n = 97)</th>
<th>All (n = 383)</th>
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<tr>
<td>1 Year</td>
<td>2 Years</td>
<td>1 Year</td>
<td>2 Years</td>
<td>1 Year</td>
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<tr>
<td>Patients with at least 1 clinical worsening event</td>
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<td>27 (28)</td>
<td>28 (15)</td>
<td>47 (25)</td>
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<td>Hospitalization for PAH</td>
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<td>20 (21)</td>
<td>22 (12)</td>
<td>35 (18)</td>
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<td>Death</td>
<td>3 (3)</td>
<td>13 (14)</td>
<td>12 (6)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Addition of approved prostacyclin analog therapy</td>
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<td>Study withdrawal because of addition of other PAH therapy</td>
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<tr>
<td>Early escape</td>
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</tr>
<tr>
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<td>0 (0)</td>
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<td>Lung transplantation</td>
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Values are n (%). Patients can be included in more than 1 category of clinical worsening. Early escape was defined by the presence of 2 or more of the following criteria: 1) a decrease of >20% in the 6-min walk distance; 2) an increase of 1 or more WHO functional class; 3) worsening right ventricular failure (as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema); 4) rapidly progressing hepatic or renal failure; and 5) refractory systolic hypotension (systolic blood pressure <85 mm Hg). All data are presented by randomized ambrisentan dose.

Abbreviations as in Table 1.

Figure 4 Kaplan-Meier Survival Analysis by Randomized Ambrisentan Dose and by All Treatment Groups Combined

Kaplan-Meier survival analysis by randomized ambrisentan dose (dashed lines) and by all treatment groups combined (solid line), with point estimates of survival shown for years 1 and 2 (all treatment groups combined). The number at risk at each time point is presented below the graph. ABS = all ambrisentan treatment groups combined.
Current medical therapies approved for the treatment of PAH have shown efficacy and safety in relatively short-term (12 to 18 weeks) randomized placebo-controlled studies. Most long-term PAH studies to date, however, have been nonrandomized observational trials focused primarily on mortality and safety, with very limited descriptions of clinical efficacy that are often restricted to selective post hoc subgroup analyses (2,17–21). Given that 6MWD has been the primary end point for nearly all pivotal PAH trials, surprisingly few long-term 6MWD data have been published, and previous reports of long-term clinical efficacy have been primarily limited to completers analyses of observed data for patients who remained on therapy at a certain time point (1,22–25). Although informative, these types of analyses can lead to overestimation of the treatment effect because they only include data for patients who have successfully remained in the trial.

In 12-week placebo-controlled studies, the ETA-selective ERA ambrisentan improved several important clinical parameters in patients with PAH, such as exercise capacity and clinical worsening (16). The current study describes long-term clinical response, disease progression, survival, and safety over a 2-year treatment period for all patients who received ambrisentan in the ARIES trials.

Of the 3 doses of ambrisentan used in this long-term study, the 2 higher doses (5 and 10 mg once daily) seemed to provide a sustained benefit in exercise capacity and dyspnea, whereas the 2.5-mg dose seemed less effective. These results are consistent with the dose-response trends that were observed for 6MWD in both of the 12-week placebo-controlled studies and the regulatory approval of the 5- and 10-mg doses for use in PAH patients.

Considering the progressive nature of the disease, it is notable that most patients maintained or had an improvement in WHO functional class and did not experience clinical worsening during 2 years of ambrisentan treatment. In the previous 12-week trials, a statistically
significant improvement compared with placebo in the pre-defined end point of time to clinical worsening was observed in the ARIES-2 study but not in the ARIES-1 study (16); however, similar estimates of clinical worsening were observed for these study subpopulations during this 2-year treatment period. This is most likely because the differences in statistical significance previously reported were largely caused by variability in the response of the placebo groups in the ARIES-1 and -2 studies (91% and 78%, respectively), as similar responses were observed in these studies for patients receiving active therapy (96% and 95%, respectively).

Kaplan-Meier estimates of 1- and 2-year survival in this study were 94% and 88%, respectively. These survival estimates are similar to the 1-year estimates previously reported by Benza et al. (26) for patients with PAH treated with sitaxsentan (96%) and bosentan (88%), as well as by McLaughlin et al. (18) and Provencher et al. (20) (89%), although these latter reports were for idiopathic PAH patients only. In the long-term follow-up of the pivotal trials for bosentan, patients with PAH associated with connective tissue disease seemed to have worse long-term survival compared with patients with idiopathic PAH (73% vs. 89%, respectively) (18,25); however, higher estimates (92%) were reported by Denton et al. (27) for connective tissue disease patients receiving bosentan in a 53-patient open-label trial. In our study, survival estimates were similar for patients with idiopathic PAH and patients with PAH associated with connective tissue disease treated with ambrisentan.

Because PAH is a progressive disease, it is not uncommon for more than 1 PAH drug to be used when patients experience clinical deterioration. However, during the 2-year treatment period of this study, the majority of patients remained at their randomized dose and received ambrisentan monotherapy; thus, the persistence of clinical benefit seen for the 5- and 10-mg dose groups seems to be primarily attributable to ambrisentan alone.

The safety profile of ambrisentan in this study was similar to that seen in the ARIES-1 and -2 trials (16). Adverse events that led to discontinuation of therapy were infrequent and were generally consistent with disease progression. Peripheral edema, a known side effect associated with ERAs, did not seem to limit treatment because most cases reported were mild to moderate and did not result in discontinuation of study drug.

In the 12-week ARIES-1 and -2 trials, no patients receiving ambrisentan developed ALT/AST >3× ULN, compared with 3 (2.3%) patients receiving placebo (16). In this 2-year follow-up study, the annual incidence of aminotransferase abnormalities was approximately 2% (16). Although this annual incidence was low, 12 patients did experience elevations >3× ULN and 2 patients discontinued because of aminotransferase abnormalities; therefore, monitoring of liver function is still advised. Consistent with previous reports with ERAs (16,28) (Actelion Pharmaceuticals Ltd., Tracleer [bosentan] tablets, U.S. Food and Drug Administration drug product label, 2009), a reduction in mean hemoglobin concentration was observed with ambrisentan treatment. This reduction manifested within the first few weeks of drug initiation, with little additional change with long-term treatment. Therefore, hemoglobin levels should be measured before initiation of ambrisentan treatment, after 4 weeks of treatment, and peri-
odically thereafter. No clinically relevant changes in international normalized ratio or warfarin dosage were observed in this study. This observation is similar to what has been observed with bosentan (Actelion Pharmaceuticals Ltd., Treacle [bosentan] tablets, U.S. Food and Drug Administration drug product label, 2009), whereas increases in international normalized ratio and/or changes in warfarin dosage have been reported with sitaxsentan, a known inhibitor of cytochrome 2C9 (28,29).

This study was not placebo controlled because monotherapy studies longer than 12 to 16 weeks have not been appropriate in PAH patients; thus, it is not possible to precisely estimate the long-term treatment effects of ambrisentan. However, in the ARIES-1 and -2 trials, the placebo groups deteriorated from baseline after 12 weeks, and considering the progressive nature of PAH, it is not unreasonable to assume that these patients would have continued to deteriorate with long-term placebo treatment. Therefore, the improvements observed in this long-term study likely represent conservative estimates of treatment effect compared with what would be expected without therapy (i.e., long-term placebo treatment).

As described earlier, previous studies that have examined long-term efficacy have generally reported observed data at specific time points (i.e., a completers analysis) without imputation for missing data (20,22,23). In this study, the primary analysis used a last observation carried forward approach for imputation of missing efficacy data. This approach allows data to be analyzed for all patients who participated in the study, not only patients who have remained on treatment. However, this approach is not without limitations. Although it is true that patients who worsen while receiving treatment will have this decline incorporated into the analyses of subsequent time points, it is also true that patients may have further declined if they had continued to be assessed. In addition, this approach may not account for stable (or improved) patients who experience an acute worsening event (e.g., death) without previous decline. Nevertheless, the observation that the 1- and 2-year 6MWD was lower with the last observation carried forward analysis than with the observed case analysis indicates that the last observation carried forward method represents a more conservative estimate of clinical benefit in this patient population.

Conclusions

The long-term use of ambrisentan over a 2-year period resulted in sustained improvements in exercise capacity and dyspnea, a stabilization of WHO functional class, a low risk of clinical worsening and death, and an acceptable safety profile that was similar to that seen in the 12-week placebo-controlled trials. These data support the use of ambrisentan as part of a long-term strategy for the treatment of patients with PAH.

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REFERENCES


Key Words: ambrisentan ● exercise capacity ● endothelin ● hypertension ● pulmonary ● long-term survival.

APPENDIX

For a complete list of investigators and centers in the ARIES-1 and -2 Study Group, please see the online version of this article.