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# Frequency of Edema in Patients With Pulmonary Arterial Hypertension Receiving Ambrisentan

**Shelley Shapiro, MD, PhD**, **David M. Pollock, PhD**, **Hunter Gillies, MD**, **Noreen Henig, MD**, **Martine Allard, PhD**, **Christiana Blair, MSc**, **Crystal Anglen, PhD**, and **Donald E. Kohan, MD, PhD**

Shelley Shapiro: Sshapiro@ucla.edu

Edema is a common side effect of endothelin receptor antagonists. Ambrisentan is an endothelin type A-selective endothelin receptor antagonist approved for the treatment of pulmonary arterial hypertension. We examined the clinical outcomes of patients who developed edema with and without ambrisentan treatment in 2 phase III, randomized placebo-controlled trials, ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2 (ARIES-1 and ARIES-2) (n = 393). Edema-related adverse events were extracted using broad adverse event search terms. The present post hoc analysis included 132 placebo patients and 261 ambrisentan patients. Of these patients, 14% of the placebo patients and 23% of the ambrisentan patients experienced edema-related adverse events. Overall, the patients who experienced edema tended to have a worse baseline World Health Organization (WHO) functional class (edema 76%, WHO functional class III–lIV; no edema 56%, WHO functional class III–IV). In the ambrisentan patients, those with edema were older (mean age 58 ± 13 years) and heavier (mean weight 75 ± 19 kg) than those without edema (mean age 49 ± 15 years; mean weight 70 ± 17 kg). At week 12 of treatment, the ambrisentan patients had significantly increased their 6-minute walk distance (6MWD) by 34.4 m compared to the placebo patients in whom the 6MWD had deteriorated by −9.0 m ($p < 0.001$). Among the ambrisentan patients, those without edema had a 6MWD increase of 38.9 m and those with edema had a 6MWD increase of 19.4 m. Ambrisentan significantly improved the brain natriuretic peptide levels by −34% compared to the brain natriuretic peptide levels in the placebo group that had worsened by +11% ($p<0.001$). Ambrisentan reduced the brain natriuretic peptide concentrations similarly in patients with and without edema. In conclusion, the present subanalysis of patients with pulmonary arterial hypertension has revealed that ambrisentan therapy provides clinical benefit compared to placebo, even in the presence of edema.

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease resulting in changes in pulmonary hemodynamics leading to increased vascular resistance and subsequent right-sided heart failure.[1 and 2] Ambrisentan is a selective type A endothelin (ET) receptor antagonist (ERA) approved for the treatment of PAH. Edema is a common side effect of ERAs. The development of edema during ERA therapy might limit its use and effectiveness;



Corresponding author: Tel: (310) 268-4314; fax: (310) 268-4260.

therefore, we analyzed data from 2 phase III, randomized, placebo-controlled trials, ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2 (ARIES-1 and ARIES-2) (n = 393) to help understand the potential risk factors for developing edema and the effect of edema on the clinical outcomes with ambrisentan treatment. The combined ARIES-1 and ARIES-2 published clinical data have shown an overall rate of peripheral edema of 17% in ambrisentan-treated patients (n = 261) compared with 11% in placebo patients (n = 132).[3] In the present subanalysis, we examined the baseline characteristics and clinical outcomes of the patients who developed edema, characterized by a broader definition, with and without ambrisentan treatment in the ARIES-1 and ARIES-2 studies.

## Methods

We randomized patients with World Health Organization group I PAH and who had received treatment in 2 concurrent placebo-controlled phase III trials: ARIES-1 (n = 201) and ARIES-2 (n = 192). The full methods and results for both of these studies have been previously published.[3] Patients received either placebo or ambrisentan at oral doses ranging from 2.5 to 10 mg/day for 12 weeks. The primary end point for both studies was the change from baseline in the 6-minute walk distance (6MWD) at week 12. The secondary end points included in this study and relevant to the present subanalysis included brain natriuretic peptide (BNP), the Borg Dyspnea Index (BDI), and World Health Organization (WHO) functional class.

To retrospectively capture and quantify those subjects who experienced any form of edema in the combined trial data, we queried the databases using adverse event search terms related to edema, including peripheral edema, edema, pitting edema, gravitational edema, localized edema, anasarca, fluid retention, and fluid overload. The edema search terms used in the present analysis varied from the original published clinical trial results in which peripheral edema was the only search term used for edema adverse event rates.[3]

The demographic and baseline characteristics were summarized by treatment group and by subjects with or without edema adverse events within the treatment groups. Differences between treatment groups in the change from baseline at week 12 in 6MWD, BNP, and BDI were analyzed using the Wilcoxon rank-sum test stratified by disease etiology (idiopathic PAH vs nonidiopathic PAH) and study (ARIES-1 vs ARIES-2). Prespecified comparisons were made between the combined ambrisentan group and placebo group. Post hoc comparisons were made between (1) the combined ambrisentan group and the placebo group within the subset of subjects with edema, (2) the combined ambrisentan group and the placebo group within the subset of subjects without edema, and (3) the combined ambrisentan subjects with edema and all placebo subjects (with or without edema). For 6MWD and BDI, point estimates and 95% confidence intervals for change from baseline to week 12 were estimated using least squares means and standard errors from 1-way analysis of variance. For BNP, the geometric mean and 95% confidence intervals for baseline and week 12 and the geometric mean ratios and 95% confidence intervals for the change from baseline to week 12 were constructed using the mean and standard errors based on the log

values and log change values, respectively. The change from baseline in WH 0 functional class is presented categorically and was analyzed with a 7-point scale: −3, −2, −1 (improved), 0 (no change), 1,2, and 3 (deteriorated) using the Wilcoxon rank-sum test. The risk of edema by dose group was evaluated by the baseline estimated glomerular filtration rate quartiles.

## Results

Using the newer broadened search terms for edema, fewer placebo patients (14.4%) compared to ambrisentan patients (23.0%) experienced edema as an adverse event in the combined ARIES-1 and ARIES-2 trials (n = 393; Table 1). Serious adverse events of edema were reported by 2 (0.8%) of 261 subjects in the ambrisentan group and 1 (0.8%) of 132 subjects in the placebo group. Edema adverse events leading to study drug or study discontinuation were reported by 1 (0.4%) of 261 subjects in the ambrisentan group and 3 (2.3%) 132 subjects in the placebo group. Most adverse events of edema were graded as mild to moderate in severity, with a similar incidence between treatment groups (ambrisentan 93% and placebo 95%). At baseline, regardless of the treatment assignment, the patients who experienced edema tended to be women (86%) and to have worse WHO functional class (75% WHO functional class III–IV) compared to patients who did not experience adverse events of edema (77% women and 56% WHO functional class III–IV). In patients taking ambrisentan, those who reported edema were older (mean age 58 ± 13 years) and heavier (mean weight 75 ± 19 kg) than those without edema (mean age 49 ± 15 years; mean weight 70 ± 17 kg). Elderly patients (age ≥65 years) taking ambrisentan had a heightened risk of edema (Table 1). Also, 50% of patients were taking diuretics at baseline and 55% of patients had received diuretics as concomitant medication at some point after baseline through week 12. No obvious relation was found between diuretic use before or during the trial and the development of edema.

For the combined ARIES trials, the baseline 6MWD for the placebo- and ambrisentan-treated patients was comparable (Table 1). The changes from baseline at week 12 in outcomes by the presence or absence of edema are listed in Table 2. Patients receiving ambrisentan significantly increased their 6MWD compared to those taking placebo ($p < 0.001$). Ambrisentan patients who experienced edema improved their 6MWD at week 12 despite the lower baseline 6MWD values compared to those who did not experience edema (323 ± 79 m vs 353 ± 80 m, respectively). However, ambrisentan patients who did not experience edema had a greater increase in the 6MWD. The baseline plasma BNP concentrations were comparable between the placebo and ambrisentan groups (Table 1). At week 12, patients receiving ambrisentan had significantly improved BNP levels compared to patients taking placebo, whose levels had deteriorated ($p < 0.001$). Among the ambrisentan patients, a reduction in BNP concentrations was observed in both patients with edema ($p = 0.058$) and without edema ($p < 0.001$) compared to the placebo patients. An improvement was still seen in the 6MWD ($p = 0.032$) and BNP levels ($p = 0.013$) in the ambrisentan patients with edema compared to the overall placebo patients (Table2). In addition, the WHO functional class deteriorated for 14% more placebo patients at week 12 compared to the ambrisentan patients. In the ambrisentan group, 4.5% more patients with edema had a deterioration in WHO functional class compared to those without edema.

Almost 50% of the study population had an estimated glomerular filtration rate <72 ml/min/1.73 $m^2$, highlighting the prevalence of renal impairment and increasing the potential importance when considering contributors to the etiology of edema. However, observation across the ambrisentan dose groups did not suggest renal impairment as a factor in ambrisentan-related edema, although the sample size might have been too small to draw definitive conclusions (Table 3).

## Discussion

Our post hoc analysis demonstrated that, although a portion of patients receiving ambrisentan developed edema of any severity, these patients still achieved a clinical benefit, as evidenced by the significantly increased 6MWD, decreased BDI scores, reduced BNP, and improved WHO functional class at week 12 compared to the placebo patients who developed edema (Table 2). Given the predominance of women in the study, and in the PAH population in general, it is difficult to determine whether female gender constitutes a risk factor. Edema was more likely to occur in patients taking ambrisentan who were older and heavier. Furthermore, edema was associated with worse functional class in both placebo and ambrisentan groups at baseline (Table 1), suggesting that more severe PAH is a major precipitant of edema, independent of treatment.

In the overall population, a reduction occurred in BNP ($p < 0.001$) in the ambrisentan group compared to the placebo group, and in the post hoc subgroup analysis, those ambrisentan subjects with edema showed a trend in the same direction ($p = 0.058$). This would suggest that, in the ambrisentan population, the mechanism for the presence of edema is unlikely to be cardiac dysfunction. In contrast, the edema observed in the placebo group indicated worsening disease and the development of heart failure, as evidenced by a decline in the 6MWD, an increase in BNP levels, and a greater rate of discontinuation of therapy in the placebo group versus the ambrisentan group.

Although fluid retention and edema are common in patients with PAH, irrespective of drug therapy, certain mechanisms in severe PAH could likely result in clinically relevant fluid retention and edema.[4,5,6,7 and 8] Even if efficacy is maintained, the development of edema can result in poor patient tolerance. Treatment with diuretics is reported to improve edema in patients with PAH.[7 and 8] Because the vast majority of ET receptors are expressed in the medullary collecting duct of the kidney, it is highly likely, albeit unproved, that ERAs induce fluid retention within the renal medulla. A recent in vivo study in rats demonstrated intravascular volume expansion from an ERA (sitaxsentan) that resolved using furosemide or chlorothalidone[9]; however, clinical studies in patients with PAH taking diuretics are warranted to provide better clinical guidance.

One of the most common adverse effects shared by ERA therapies in PAH is peripheral edema.[3 and 10] ET-1 induces natriuresis and diuresis through ET type B receptors; thus, the blockade of these receptors can result in fluid retention.[11 and 12] However, ET type A receptors can also modulate renal salt and water excretion. Preclinical studies on collecting duct ET receptors suggest the potential for fluid retention through blockade of the ET type A receptor.[13, 14 and 15] Additional mechanisms, although speculative, by which ERAs might

induce edema could include unopposed precapillary arteriolar vasodilation and changes in capillary permeability Hence, a combination of primary vascular and renal effects of ET type A blockade might account for the fluid retention induced by this class of agents.

Aside from the association of edema with ERA use, edema is 1 of the cardinal signs of PAH and might be an indication of right-sided heart failure, worsening PAH, or nonadherence to therapy.[4 and 5] Furthermore, it can be difficult to distinguish the various etiologies of edema, which could be due to worsening right-sided heart function, concomitant drug side effects, dietary indiscretion, or inadequate diuretic therapy.

In conclusion, in the ARIES-1 and –2 trials, patients taking ambrisentan exhibited improvements in 6MWD and BNP levels compared to the placebo patients, regardless of whether they experienced edema. Early recognition of edema and prompt diuretic management while continuing ambrisentan therapy might enhance the benefit of ambrisentan in those subjects prone to edema.

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**Table 1**

Population baseline demogrphics and characteristics (n=393)

| Demographics and Baseline Characteristic | Overall Placebo (n=132) | Overall Ambrisentan (n=261) | Placebo (n=132) | | Ambrisentan (n=261) | |
|---|---|---|---|---|---|---|
| | | | Edema* Subgroup (n = 19; 14.4%) | No Edema Subgroup (n = 113; 86.6%) | Edema Subgroup (n = 60; 23.0%) | No Edema Subgroup (n = 201; 77.0%) |
| Women | 78% | 80% | 89% | 76% | 85% | 78% |
| White | 76% | 77% | 79% | 75% | 83% | 76% |
| Idiopathic pulmonary arterial hypertension | 64% | 64% | 63% | 65% | 58% | 65% |
| Pulmonary arterial hypertension associated with connective tissue disease | 33% | 31% | 37% | 32% | 35% | 30% |
| World Health Organization functional class III–IV | 61% | 59% | 79% | 58% | 73% | 54% |
| Age (years) | 49 ± 15 | 51 ± 15 | 49 ± 12 | 49 ± 16 | 58 ± 13 | 49 ± 15 |
| <65 | 79% | 79% | 84% | 78% | 65% | 83% |
| ≥65 | 21% | 21% | 16% | 22% | 35% | 17% |
| Weight (kg) | 74 ± 20 | 71 ± 18 | 74 ± 16 | 74 ± 20 | 75 ± 19 | 70 ± 17 |
| 6-Minute walk distance (m) | 342 ± 80 | 346 ± 81 | 346 ± 65 | 342 ± 82 | 323 ± 79 | 353 ± 80 |
| Borg Dyspnea Index score | 3.8 ± 2.2 | 3.8 ± 2.3 | 3.3 ± 1.7 | 3.9 ± 2.2 | 3.7 ± 1.9 | 3.9 ± 2.4 |
| Brain natriuretic peptide concentration (geometric mean,ng/L) | 264 ± 279 | 262 ± 375 | 284 ± 275 | 235 ± 281 | 287 ± 402 | 250 ± 347 |

Data are presented as mean ± SD or %.

*Edema included the following adverse events terms: peripheral edema, edema, pitting edema, gravitational edema, localized edema, anasarca, fluid retention, and fluid overload.

**Table 2**

Change from baseline in end points studied (n = 393)

| Variable | Overall Placebo (n = 132) | Overall Ambrisentan (n = 261) | Placebo (n = 132) | | Ambrisentan (n = 261) | |
|---|---|---|---|---|---|---|
| | | | Edema* Subgroup (n = 19; 14.4%) | No Edema Subgroup (n = 113; 86.6%) | Edema Subgroup (n = 60; 23.0%) | No Edema Subgroup (n = 201; 77.0%) |
| Δ 6-Minute walk distance (m) | | | | | | |
| Mean | −9.0 | 34.4 | −54.8 | −1.2 | 19.4 | 38.9 |
| 95% Confidence interval | −24, 5.9 | 25, 44 | −106.3, −3.4 | −16.2, 13.7 | 6.3, 32.5 | 27.3, 50.5 |
| p Value 1 | — | <0.001 | — | — | 0.002 | <0.001 |
| p Value 2 | — | — | — | — | 0.032 | — |
| Δ Borg dyspnea index score | | | | | | |
| Mean | 0.40 | −0.45 | 1.2 | 0.3 | −0.4 | −0.5 |
| 95% Confidence interval | −0.02, 0.82 | −0.69, −0.20 | 0.05, 2.38 | −0.19, 0.72 | −0.88, 0.18 | −0.75, −0.19 |
| p Value 1 | — | <0.001 | — | — | 0.07 | 0.005 |
| p Value 2 | — | — | — | — | 0.142 | — |
| Δ Brain natriuretic peptide concentration (ng/L) | | | | | | |
| % Geometric mean ratio | 11 | −34 | 47 | 7 | −28 | −35 |
| 95% Confidence interval | −6, 31 | −25, −41 | 0, 115 | −11, 27 | −42, −10 | −44, −25 |
| p Value 1 | — | <0.001 | — | — | 0.058 | <0.001 |
| p Value 2 | — | — | — | — | 0.013 | — |
| Δ World Health Organization functional class | | | | | | |
| Improved | 21% | 22% | 0% | 24% | 20% | 23% |
| No change | 62% | 74% | 63% | 62% | 73% | 75% |
| Deteriorated | 17% | 3% | 37% | 14% | 7% | 2.5% |
| p Value 1 | — | 0.011 | — | — | <0.001 | 0.104 |
| p Value 2 | — | — | — | — | 0.419 | — |

p Values are from the Wilcoxon rank-sum test stratified by disease stratification factor and study; p value 1 compares placebo and ambrisentan overall or within subgroup; p value 2 compares the plcebo overall group and ambrisentan edema group.

*Edema included the following adverse events terms: peripheral edema, edema, pitting edema, gravitational edema, localized edema, anasarca, fluid retention, and fluid overload.

**Table 3**

Presence and absence of edema by baseline estimated glomerular filtration rate quartiles (n = 393)*

| Estimated Glomerular Filtration Rate† quartile (mL/min/1.73 m$^2$) | Edema‡ | Placebo (n = 132) | Ambrisentan | | | |
|---|---|---|---|---|---|---|
| | | | 2.5 mg (n = 64) | 5 mg (n = 130) | 10 mg (n = 67) | Overall (n = 261) |
| 22.19 to ≤60.25 | | | | | | |
| | Yes | 5 (3.8%) | 3 (4.7%) | 9 (6.9%) | 7 (10.4%) | 19 (7.3%) |
| | No | 23 (17.4%) | 16 (25.0%) | 26 (20.0%) | 6 (9.0%) | 48 (18.4%) |
| 60.26 to ≤71.61 | | | | | | |
| | Yes | 8 (6.1%) | 0 (0%) | 7 (5.4%) | 6 (9.0%) | 13 (5.0%) |
| | No | 28 (21.2%) | 15 (23.4%) | 22 (16.9%) | 9 (13.4%) | 46 (17.6%) |
| 71.62 to ≤87.40 | | | | | | |
| | Yes | 2 (1.5%) | 3 (4.7%) | 6 (4.6%) | 2 (3.0%) | 11 (4.2%) |
| | No | 28 (21.2%) | 16 (25.0%) | 24 (18.5%) | 14 (20.9%) | 54 (20.7%) |
| 87.41 to ≤270.13 | | | | | | |
| | Yes | 2 (1.5%) | 1 (1.6%) | 7 (5.4%) | 7 (10.4%) | 15 (19.5%) |
| | No | 26 (19.7%) | 9 (14.1%) | 27 (20.8%) | 15 (22.4%) | 51 (19.5%) |

*Baseline estimated glomerular filtration rate missing for 14.

†Estimated glomerular filtration rate (mL/min/1.73 m$^2$) = 32,788 × serum creatinine$^{-1.154}$ (μmol/L) × age$^{-0.203}$ × [1.212 if black] × [0.742 if a woman].

‡Edema included the following adverse events terms: peripheral edema, edema, pitting edema, gravitational edema, localized edema, anasarca, fluid retention, and fluid overload.