ARIES and EARLY: ambrisentan and bosentan effective in WHO class I and II PAH

Pulmonary arterial hypertension (PAH) is a serious condition, current treatments for which are inadequate. Common therapies for this disorder are associated with critical safety, tolerability and drug-delivery issues and many trials have included only severely compromised patients. Two research groups have evaluated the efficacy of key agents in moderately compromised individuals.

The ARIES investigators conducted two studies designed to examine the efficacy of the oral, A-selective, endothelin-receptor blocker ambrisentan in patients with PAH. In ARIES-1, the efficacy and safety of 5 mg ambrisentan, 10 mg ambrisentan and placebo daily were compared in 67, 68 and 67 patients, respectively. In ARIES-2, patients were randomly allocated to receive 2.5 mg or 5 mg ambrisentan or placebo daily (64, 63 and 65 patients, respectively). At 12 weeks, 6 min walking distance—one of the primary efficacy measures and an independent predictor of mortality in patients with idiopathic PAH—had improved in all ambrisentan-treated groups from both studies. Compared with placebo, ambrisentan increased mean 6 min walking distances by 32 m for the 2.5 mg-dose group (95% CI 2–63 m; $P = 0.022$), 31 m and 59 m for the 5 mg groups in ARIES-1 and ARIES-2, respectively (95% CI 3–59 m, $P = 0.008$; 95% CI 30–89 m, $P < 0.001$), and 51 m for the 10 mg group (95% CI 27–76 m, $P < 0.001$). Additionally, in ARIES-2 and in a prespecified analysis of pooled data from both 5 mg ambrisentan-treated groups, time to clinical worsening (i.e. mortality, hospitalization or disease progression) improved in ambrisentan-treated patients compared with placebo-treated patients. Furthermore, ambrisentan was safe; no patients had serum aminotransferase levels >3× the upper normal limit. Interestingly, in ARIES-1, the WHO functional class of ambrisentan-treated patients improved significantly over the study period compared with that of placebo-treated patients ($P = 0.036$)—an important finding, as the majority of patients were classified as either WHO functional class II or III at enrollment.

The EARLY study corroborated the ARIES finding that patients with moderate PAH benefit from treatment. This study analyzed bosentan—an oral, nonselective, endothelin-receptor blocker, whose efficacy has been established only in study populations that largely comprised patients in WHO functional classes III and IV. After 6 months of bosentan treatment, patients' mean 6 min walking distance had increased from baseline by 11.2 m (95% CI –4.6 m to 27.0 m), whereas this parameter had decreased by 7.9 m (95% CI –4.3 m to 8.5 m) in placebo-treated patients. However, the difference in these values between groups was not statistically significant. At 6 months, patients in the bosentan group had a greater improvement in vascular resistance—expressed as percentages of baseline values—than those in the placebo group (83.2% versus 107.5%, 95% CI 73.8–93.7% versus 97.6–118.4%, respectively), and this difference between groups was statistically significant ($P < 0.0001$).

Taken together, these studies support initiation of drug treatment in patients with PAH before they become severely compromised. Further studies of ambrisentan are required to establish optimal dosing regimens for this drug.

Original articles Galiè N *et al.* (2008) 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. *Circulation* **117:** 3010–3019
Galiè N *et al.* (2008) Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomized controlled trial. *Lancet* **371:** 2093–2100