HYPERTENSION

Initial combination therapy improves PAH

The efficacy of initial combination therapy for the treatment of pulmonary arterial hypertension (PAH) is unknown, but previous reports have shown that combination therapy with drugs that target different mechanistic pathways might improve clinical outcomes. Investigators in the AMBITION trial sought to assess the efficacy and safety of initial combination therapy with the endothelin receptor antagonist ambrisentan and the phosphodiesterase type 5 inhibitor tadalafil in previously untreated individuals with PAH, and their findings have now been published in *The New England Journal of Medicine*.

In this multicentre, randomized, double-blind trial, patients with PAH who had not been treated with an approved therapy were randomly assigned to receive 10 mg of ambrisentan plus 40 mg of tadalafil (combination-therapy group), 10 mg of ambrisentan plus placebo (ambrisentan-monotherapy group), or 40 mg of tadalafil plus placebo (tadalafil-monotherapy group) in a 2:1:1 ratio. The primary end point was the first incident of clinical failure, defined as a composite end point of death from any cause, hospitalization for PAH, progression of disease, or unsatisfactory long-term clinical response. Disease progression and clinical response were based on measures of changes in baseline 6-min walking distance in combination with WHO functional class III or IV symptoms.

In total, 500 participants were included in the primary analysis, and 123 patients had a primary end point event during the study period, including 46 (18%) in the combination-therapy group compared with 77 (31%) in the pooled-monotherapy group (HR 0.50, 95% CI 0.35–0.72, $P < 0.001$). An analysis of secondary efficacy end points further demonstrated the benefit of combination therapy compared with ambrisentan or tadalafil monotherapy. The combination-therapy group, when compared with the pooled-monotherapy group, had reduced levels of N-terminal pro-brain natriuretic peptide (mean change, -67.2% versus -50.4% ; $P < 0.001$), an increased proportion of patients with a satisfactory clinical response (39% versus 29%; OR 1.56, 95% CI 1.05–2.32, $P = 0.03$), and an improvement in 6-min walking distance (median change from baseline, 48.98 m versus 23.80 m; $P < 0.001$). Importantly, peripheral oedema, headaches, nasal congestion, and anaemia were more common among patients receiving combination therapy than in patients in either monotherapy group, but the rate of severe adverse events was not significantly different between the treatment groups.

“Thanks to this study,” explains Nazzareno Galiè, the lead investigator of the AMBITION trial, “initial oral double combination therapy has now been included in the Joint 2015 ESC and the European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension. [This treatment is] considered today the standard of care in treatment-naïve patients.” Given that the risk of the primary end point of clinical failure was 50% lower in the combination-therapy group than with monotherapy with either drug, the study investigators conclude that “the AMBITION trial supports the rationale for targeting multiple pathways in pulmonary arterial hypertension and showed that early combination therapy can be beneficial”.

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