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AMBITION fulfilled: initial combination therapy is more efficacious than monotherapy in PAH

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The AMBITION (Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension) study by Galie et al, published this summer, demonstrates that up front oral combination therapy in patients with group 1 pulmonary hypertension, pulmonary arterial hypertension (PAH), is superior to initial monotherapy [1]. This approach to treating PAH was suggested 13 years ago, and while many investigators and clinicians have employed add-on therapy, that is starting with initial oral monotherapy and adding a second oral agent if certain goals are not achieved or patients worsen, the data from randomized studies to support this approach, has not been mixed, but overall not very impressive [2-6]. Conversely, AMBITION provides strong support for initial treatment with combination oral therapy in patients with PAH. Based on the results of this study, the FDA has this month approved initial combination therapy for patients in the United States with PAH.

AMBITION was a large, multicenter study that evaluated 500 functional class 2 and 3 patients, 253 of whom received combination therapy, 126 ambrisentan monotherapy and 121 tadalafil monotherapy. Unlike the vast majority of clinical trials in PAH that have been 12 or 16 week studies usually with an exercise and/or hemodynamic endpoint, this was an event-driven study, allowing a much longer observation of study participants: mean duration of use of those initially assigned combination therapy was 550 days and in the pooled monotherapy groups was 484 days. The primary end point in a time-to-event analysis was the first event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response.

The results were quite impressive in favor of combination therapy with the primary endpoint occurring in 18% of those receiving combination therapy compared to 31% in the pooled monotherapy groups giving a hazard ratio of 0.50, 95% confidence interval, 0.35-0.72, $P<0.001$. The separation in the curves between the two groups was evidence as early as 24 weeks. Pre-specified secondary endpoints were also assessed after 24 weeks and demonstrated results in favor of the combination group. This included greater reductions in N-terminal pro-brain natriuretic peptide levels, greater improvement in six-min walk distance and a higher percentage of patients with a satisfactory clinical response, $P<0.05$ for all three endpoints. There was no

difference in functional class improvement, although given the limitation to functional class 2 and 3 patients, this is not very surprising. With regard to side effects, there was more edema, headaches and nasal congestion in the combination group; however, the rate of serious adverse events and discontinuation of study drug was similar in all 3 arms of the study.

There are caveats to this study, however. First, the benefit of combination therapy seen with the primary endpoint was driven almost entirely by a greater percentage of patients requiring hospitalization for worsening PAH in the monotherapy groups; there was no mortality benefit from combination therapy. Second, the results may not extend to other combinations of PDE5Is and ERAs, or other drug combinations of PAH approved therapies. In the only other upfront combination therapy study, BREATHE-2, comparing monotherapy with intravenous epoprostenol to initial combination therapy with epoprostenol and bosentan, no benefit was demonstrated and there were more deaths in the combination group, although the study was under-powered and involved a very sick group of patients [7]. Third, we do not know if there is a benefit with functional Class I patients or whether Class IV patient requiring continuous prostaglandin therapy should receive combination oral therapy as well. The Paces study, evaluating the addition of sildenafil to patients on stable doses of epoprostenol, showed improvement in exercise capacity, hemodynamics and survival, suggesting that combined initial treatment with prostaglandin therapy and a PDE5I is likely to be of greater benefit than prostaglandin therapy alone [8]. There are, however, no studies to guide us on the use of triple combination therapy, either as initial or as add on treatment. Despite these limitations and the need for additional combination drug studies, AMBITION provides strong support for using combination oral therapy as initial treatment in large portion of patients with PAH and the basis for a shift in the treatment paradigm of PAH.

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