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Hit Early and Hit Hard in Pulmonary Arterial Hypertension? Not So Fast!

Despite significant recent progress in medical therapy, pulmonary arterial hypertension (PAH) remains a severe disease with no cure. Effective medical treatment started with calcium channel blockers for the very few patients with idiopathic disease who displayed acute vasodilator response (1). This step forward was followed rapidly by therapy targeting one of the three classical pathways implicated in the pathogenesis of PAH (the endothelin, nitric oxide, and prostacyclin pathways) (2). The success of oral monotherapy targeting one pathway was followed by dual therapy targeting two separate pathways in either sequential or upfront combination modality (3, 4), a logical step akin to strategies employed in other cardiovascular or neoplastic diseases. With this paradigm shift, it was given that the next intervention for this lethal disease would be therapy targeting all three known pathogenic pathways (5), an approach often adopted clinically without the availability of strong scientific data. Although survival has improved for patients with PAH, many questions remain unanswered: should treatment with three agents immediately after diagnosis be recommended as suggested by some studies (6)? Should “the hit early and hit hard” approach using this three-pronged approach be the new norm? Alternatively, is one of these pathways predominantly pathogenic in a given individual and, as such, the most important early target?

In this issue of the *Journal*, Boucly and colleagues (pp. 842–854) examined, in this context, the impact of initial treatment strategy on long-term survival in PAH (7). The study consisted of a retrospective analysis of 1,611 patients with incident idiopathic, heritable, or

anorexigen-induced PAH. Survival was assessed according to initial monotherapy, dual therapy, or triple therapy. The authors concluded that overall survival was better with triple combination compared with monotherapy or dual combination therapy, particularly in high-risk patients. In multivariate Cox regression, initial triple combination therapy including parenteral prostacyclin was independently associated with better survival.

Despite the retrospective nature of this study, the findings have potentially important implications. The treatment cohorts are well defined, and the focus on a limited large subgroup of patients with Group 1 PAH is an obvious strength. There are, however, several concerns about the findings and their clinical implications. The multivariable Cox analysis suggests an “independent effect” of younger age, female sex, and triple combination therapy. It is noteworthy that the patients treated with triple combination were nearly two decades younger than those treated with monotherapy or dual combination therapy. They also tended to more likely be female patients (both younger age and female sex carry better prognosis in PAH). They had more severe hemodynamics compared with the other two groups but were also more likely to have a good response to initial therapy. In addition, their comorbid conditions were less than half those of the other two groups. It is, therefore, risky and incongruous for the authors to conclude, based on a retrospective study, that triple combination therapy may equally apply to all patients with PAH, particularly older males with multiple comorbidities. To their credit, however, the authors did perform a propensity score analysis to match triple therapy patients for confounding factors (e.g., age and sex, which might influence treatment selection) and showed similar results compared with those observed in the entire population. Although this is reassuring, the combination of three vasodilators could still be poorly tolerated in older patients with cardiac or other comorbid conditions. This significant limitation of the study was acknowledged by the authors.

As the French registry enrolled patients from multiple centers, it is surprising that differences in center practices and regimens (e.g.,

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use of systemic prostacyclin and upfront triple combination) or differences in types of patients and comorbid conditions that may influence phenotyping were not detailed and discussed. Although the strength of the centralized French registry is evident, phenotyping and potential bias by individual centers may be an issue here.

Another obvious question is the effect of timing or epoch studied on survival. The study includes patients treated over a period of 14 years, a time during which treatment for PAH, both targeted and supportive, has evolved significantly and has been associated with marked improvement in overall survival. The authors note that only the initial treatment modality was included in the multivariable analysis; this is another significant limitation of the analysis, as it is highly likely that many patients had a change in therapy or added therapies during the study.

Finally, the negative results of the recently completed The Efficacy and Safety of Initial Triple versus Initial Dual Oral Combination Therapy in Patients with Newly Diagnosed Pulmonary Arterial Hypertension (TRITON) trial (5) should be an additional cautionary tale despite the fact that this trial consisted of patients on triple oral therapy but excluded patients receiving intravenous prostacyclin or those patients in Functional Class IV. Although the study by Boucly and colleagues does have some very interesting observations with potentially important implications, the question of triple therapy effectiveness, particularly one including initial prostacyclin treatment, remains unanswered and will only be assessed in a large, well-controlled, prospective clinical trial. ■

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⊕ Upfront Combination Therapy for Pulmonary Arterial Hypertension: Time to Be More Ambitious than AMBITION

Modern treatment algorithms for pulmonary arterial hypertension (PAH) using multiparametric risk stratification have improved outcomes for patients with PAH (1). Currently, treatment algorithms propose upfront triple combination therapy, including a parenteral prostacyclin, for high-risk patients, citing observational studies (2), and upfront dual oral combination therapy for the majority of low- and intermediate-risk patients based on the Ambrisentan and

Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial, which demonstrated a 50% relative risk reduction for time to clinical failure with combination therapy (3).

In this context, in this issue of the *Journal*, Boucly and colleagues (pp. 842–854) present a retrospective cohort study evaluating the association between initial treatment strategy and survival among patients with newly diagnosed PAH using the French PH Registry (4). The study included 1,611 patients, of whom 984, 551, and 76 were treated with an initial strategy of mono, dual, or triple therapy with a parenteral prostacyclin and were followed for a median of 32 months. The primary outcomes were overall survival and transplant-free survival. The triple therapy group was younger with fewer comorbidities but more severe PAH. Triple therapy was associated with improved survival (91% vs. 61%) and transplant-free survival

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