When more is more: the role of additional upfront therapy in pulmonary arterial hypertension

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Shareable abstract (@ERSpublications)
Early combination therapy targeting several relevant pathogenic pathways, including the prostacyclin pathway, is likely to be of benefit to most patients with PAH https://bit.ly/3GisHnA

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Pulmonary arterial hypertension (PAH) is a rare disease characterised by pulmonary vascular remodelling and related increased pulmonary vascular resistance. This disease, if left untreated, will ultimately lead to death from right ventricular failure [1]. Currently available therapies target one of three known pathogenic pathways: the endothelin, prostacyclin or nitric oxide pathway [2, 3]. The current treatment paradigm emphasises the role of upfront combination therapy, although the permutation and timing of which remain unclear [4]. Despite advances in the understanding and treatment of this disease, mortality from PAH remains unacceptably high [5]. Ongoing investigation into drug combination strategies and timing of therapy initiation provides clinicians and patients with the opportunity to maximise benefit from currently available therapies, as novel drug discovery can take decades.

Selexipag, an oral prostacyclin receptor agonist, is primarily used in patients with moderate to severe disease as an adjunct to background therapy typically consisting of a phosphodiesterase inhibitor and endothelin receptor antagonist [3]. The role for upfront selexipag in combination triple therapy remains unclear. In this issue of *ERJ Open Research*, Coghlan *et al.* [6] present pooled patient data from two large, multicentre randomised controlled trials to investigate the impact of early selexipag therapy on PAH disease progression and survival. A total of 649 patients previously enrolled in the GRIPHON [7] and TRITON [8] studies were pooled such that those randomised to receive selexipag were in the pooled selexipag group and those randomised to receive placebo were in the control group. Disease progression events were defined by the original trials but generally included hospitalisation or clinical worsening due to PAH, and death. Cox proportional hazard regression was performed using patient characteristics, region, functional and biological markers of disease, and original study as covariates. Notably, the majority of patients were on at least monotherapy at trial enrolment, and 44% in both groups were on double therapy with an endothelin receptor antagonist and a phosphodiesterase inhibitor. To adjust for this, the authors performed additional sensitivity analyses using a similar model but included the use of background therapy as a time-dependent covariate. Median patient follow-up time was similar in both groups: 25.0 months for the pooled selexipag group and 24.2 months for the pooled control group. The results of this study indicate that early initiation of selexipag reduced time to first disease progression by 52% compared to control patients, primarily by reducing the time to first hospitalisation for and/or clinical worsening of PAH. The effect was maintained in patients on dual background therapy, suggesting an effect of selexipag distinct from other PAH therapies. Compared with controls, patients in the pooled selexipag group had a trend towards reduced hazard ratio for all-cause death up to the end of the study (0.70, 95% CI 0.45–1.10), a finding demonstrated in *post hoc* analyses of the individual studies, GRIPHON [9] and TRITON [8], as well.

The methods used in this work appear to be statistically comprehensive. The authors have selected studies for pooled analysis that were fairly similar in study design and end-points. Description of the methodology

and analyses to confirm appropriateness of pooling the data is easily accessible. Data were combined at the individual-patient level. Differences in censoring at the study level were addressed and, we are told, are unlikely to have impacted the results.

This work highlights the importance of clinical trial design, especially in rare diseases such as PAH, in which historically, short-term (12–24 week) primary end-points like 6-min walk distance are evaluated in small groups of patients [10]. Unfortunately, as the study authors note, this leaves these large, multicentre randomised controlled trials underpowered to address long-term clinical benefit. Pooling data from clinical trials at the individual-patient level enables researchers to identify potential differences in longer-term meaningful outcomes.

In this analysis, Coghlan *et al.* [6] suggest that early focus on the prostacyclin pathway with oral selexipag therapy improves time to clinical worsening, a notion, albeit with parenteral prostacyclin therapy, that was also demonstrated in a retrospective analysis in patients enrolled in the French Pulmonary Hypertension Registry [11]. It is important to note, however, that in both GRIPHON [7] and TRITON, selexipag dosing was started low and increased weekly to a high goal dose (1600 mg twice daily) or patient tolerance. In GRIPHON, ∼54% of patients, and in TRITON, ∼50% of patients, were unable to achieve high-dose therapy. This is presumably due to intolerable side-effects, given the study protocols. The implication that many patients did not reach high therapeutic selexipag dosing in the current study is two-fold. First, patients in the pooled selexipag group received varying doses of medication and, thus, a detailed analysis of outcome stratified by dose might be of value. Secondly, in a broader sense, if early selexipag therapy does improve long-term patient outcomes and even reduce death, this would have to be weighed against adverse side-effects of the drug as part of combination therapy. While the current work does describe pooled adverse side-effects and safety events, it is difficult to attribute these to one specific therapy given the high prevalence of background therapy in addition to the aforementioned selexipag. This type of analysis is likely outside the scope of the current investigation but should be considered in future pooled *post hoc* analyses. Similarly, a cost comparison analysis in future work would be interesting given the incredible cost of PAH therapies [12].

These issues are increasingly central to the treatment paradigm when evaluating the benefit of upfront combination PAH therapies and, notably, are not unique to PAH. Throughout the literature in left heart failure, specifically in heart failure with reduced ejection fraction, there are well documented issues with achieving target drug doses in clinical trials and high reports of adverse side-effects among patients receiving both drug and placebo [13]. This is important as we consider the value of each additional medication to target different underlying mechanisms in PAH. Even more so, as additional pathways are identified and new therapies become available, such as the novel fusion protein sotatercept, which targets the bone morphogenic protein pathway [14–16]. Are we slowly progressing from triple therapy to quadruple therapy? The clinical experience in left heart failure should be a cautionary tale that multiple upfront drug therapies can be complex for patients and providers. Nevertheless, targeting multiple relevant pathways appears to be clinically beneficial.

Significant work within the basic science and translational realms is underway to better characterise PAH patients and disease in an effort to improve individualised treatment strategies. Meanwhile, early combination therapy targeting several relevant pathogenic pathways, including the prostacyclin pathway, is likely to be of benefit to most patients.

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