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Editorial Comment: "Could We Maintain the Initial Efficacy of Triple Sequential Combination Therapies with Selexipag Against Progressive Deterioration Risk in Patients with Pulmonary Arterial Hypertension: Insights from a Single-Centre Study"

EDITORIAL COMMENT

Pulmonary arterial hypertension (PAH) remains a progressive, fatal disease characterized by progressive increase in pulmonary vascular resistance leading to right ventricular failure. While modern pharmacotherapy targets the endothelin, nitric oxide, and prostacyclin pathways, the timing of therapeutic escalation remains a subject of intense clinical debate. The recent original investigation published in *The Anatolian Journal of Cardiology* offers compelling real-world evidence suggesting that the efficacy of the oral IP receptor agonist selexipag is tightly linked to the patient's risk status at the time of initiation, thereby advocating for a paradigm shift toward earlier intervention.[1]

The retrospective single-center study analyzed 127 patients receiving sequential triple therapy including selexipag. The authors observed that while selexipag elicited significant initial improvements in functional class, 6-minute walk distance, and echocardiographic parameters (such as TAPSE) during the first 12 months, these benefits appeared to attenuate in the longer term.[1] Crucially, the study demonstrated that long-term survival was not dependent on the maximum achieved dose of the drug. Instead, mortality was independently predicted by baseline risk scores—specifically the SPAHR, REVEAL 2.0, and REVEAL Lite 2.0 scores—at the moment selexipag was introduced.

These findings underscore a critical clinical axiom: the window of opportunity to alter the disease trajectory is narrow. The study noted a substantial delay in treatment escalation, with a mean time delay for combining selexipag with background therapies of over 1700 days. The authors suggested that the observed attenuation of benefit after one year likely reflects the "progressive deteriorating nature of the disease" rather than a loss of drug efficacy. Consequently, delaying triple therapy until a patient creates a high-risk profile significantly diminishes the survival benefit, regardless of the dose titrated.

This "earlier is better" concept is strongly supported by the broader literature. The pivotal GRIPHON randomized clinical trial established that selexipag reduces the risk of morbidity and mortality by 40%.[2] However, subsequent sub-analyses of GRIPHON data have highlighted that patients derive greater benefit when selexipag is initiated earlier on background double therapy rather than waiting for clinical deterioration.[3] Furthermore, a retrospective analysis by Tsang et al[4] demonstrated that initiating selexipag within 12 months of a PAH diagnosis was associated with reduced hospitalization rates and medical costs compared to delayed initiation.

In conclusion, the current study serves as a stark reminder that "treating to failure" is an obsolete strategy in PAH management. The correlation between lower baseline risk scores and improved survival mandates a proactive approach. Clinicians should not wait for overt right heart failure to escalate therapy. To maintain

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efficacy and improve prognosis, selexipag must be utilized not merely as a rescue therapy for late-stage disease, but as an early, integral component of sequential triple combination therapy.

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