Survival in sight: Rethinking PDE5 inhibitors in ILD-associated pulmonary hypertension

Pulmonary hypertension (PH) associated with interstitial lung disease (ILD) remains one of the most discouraging frontiers in respiratory medicine. For decades, patients have slipped through the narrow space between two devastating pathologies - the scarring of lung tissue and the rise of pulmonary pressures with consequent cardiac strain. Despite a growing list of targeted therapies for pulmonary arterial hypertension (PAH), none have convincingly altered outcomes in ILD-PH. Until now, the focus had been on modest gains in exercise capacity and patient-reported quality of life. Survival benefit felt aspirational - an endpoint always out of reach.

The recent analysis from the Pulmonary Vascular Research Institute (PVRI) GoDeep Meta-Registry may mark a turning point.[1] Among more than 34 000 patients in this international real-world cohort, 940 had hemodynamically confirmed ILD-PH - a group known for poor outcomes. The investigators stratified patients by pulmonary vascular resistance (PVR) and interrogated survival using rigorous statistical approaches, including Cox proportional hazards modelling and target trial emulation.

Their findings were striking. Patients with severe PH (PVR >5 Wood units) had dismal survival - only 29% alive at 3 years and 18% at 5 years, faring even worse than those with PAH. Yet among this group, treatment with phosphodiesterase-5 inhibitors (PDE5is) was consistently associated with significantly improved survival. Hazard ratios of approximately 0.5 across ILD subtypes, and even greater benefit when combined with inhaled prostacyclin, suggest more than statistical noise - a real and clinically meaningful effect. Importantly, these results were validated in the independent COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry, strengthening confidence in the observed association.[1]

What makes this finding so profound is its contrast to the landscape we have known. Past trials in PH-ILD, such as the STEP-IPF(Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial, evaluated sildenafil primarily for functional and quality-of-life outcomes, with limited or equivocal effects on exercise tolerance and no survival signal.[2,3] Clinicians were left to focus on symptom management, oxygen therapy, and transplant referral. Now, for the first time, we see a glimmer of survival advantage- not from a novel, expensive molecule, but from a more accessible and familiar therapy already available across much of South Africa.

In resource-limited settings, this accessibility matters. PDE5 inhibitors such as sildenafil are not only widely available but also relatively affordable compared with newer biological or inhaled therapies. If their survival benefit in severe ILD-PH is confirmed in prospective trials, this could represent a rare intersection of efficacy, equity, and feasibility - a triple win rarely seen in pulmonary vascular disease.

However, the authors are careful in their interpretation, and so should we. Observational data, however sophisticated, cannot fully eliminate confounding. The benefit was confined to patients with severe hemodynamic impairment, underscoring that PH severity drives both risk and treatment responsiveness. The next challenge will be translating these findings into pragmatic clinical guidance - defining who to treat, when to start, and how to integrate PDE5i's into existing ILD management pathways without compromising gas exchange or overburdening systems already stretched thin.

Still, it is difficult not to feel a quiet optimism reading this paper. For clinicians who have spent years balancing caution with compassion in ILD-PH, it offers something new- hope anchored in data. Perhaps, as the authors suggest, survival in this population is no longer an unattainable endpoint. As we continue to refine our understanding of pulmonary vascular remodelling in fibrotic lung disease, studies like this remind us that progress does not always arrive through novel molecules. Sometimes, it comes from re-examining what we already have - and daring to believe that survival, not just stability, might finally be within reach.

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