RISE-IIP: some pitfalls and observations

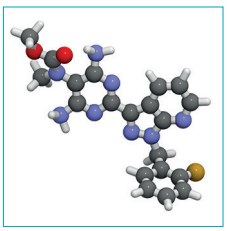
Despite disappointing negative results, the RISE-IIP study, reported by Steven D Nathan and colleagues,[1] offers an interesting opportunity to explore some aspects of future research and of the design of clinical trials in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia.

The first observation concerns the patient population selected. The authors state that: "although the clinical course and outcomes of the various idiopathic interstitial pneumonias are different, the prognosis of these conditions… is quite similar once pulmonary hypertension supervenes".[1] We do not have consistent scientific data to support this statement outside idiopathic pulmonary fibrosis and non-specific interstitial pneumonia. The prognosis of a cryptogenic organising pneumonia is quite different from that of an acute interstitial pneumonia, the same goes for other idiopathic interstitial pneumonias. The authors indicate that this broad inclusion criterion facilitates recruitment of patients, however 85% of the randomly assigned patients had idiopathic pulmonary fibrosis or non-specific interstitial pneumonia. Evaluation of these two idiopathic interstitial pneumonias together in the future would guarantee a greater homogeneity of the study population without serious difficulties in recruitment.

Another crucial aspect is the choice of the 6-minute walk distance as primary endpoint. 6-minute walk distance has not been validated in patients with parenchymal disease and pulmonary hypertension and the world symposium on pulmonary hypertension suggested that improvement of the informative value of this test in these patients is needed.[2] Composite endpoints should be seriously considered in the future.

The authors speculate that the negative outcome of these patients can be traced back to a discordant haemodynamic response with an increased cardiac output accompanied by an unaltered mean pulmonary arterial pressure. This situation, already previously described,[3] could cause an impaired workload of the right ventricle and perhaps an increased mortality risk.[1] This haemodynamic behaviour is typical of the response to riociguat in pulmonary artery hypertension. Patients never previously treated show an improvement in the cardiac index (0·61 per min per m^2), with a reduction of only 4·4 mm Hg of the mean pulmonary arterial pressure.[4] A similar response to riociguat was recorded in chronic thromboembolic pulmonary hypertension.[5]

Perhaps the main question that arises from the results of this study is whether the time has come to change the therapeutic standard and to consider shifting future trials on class III pulmonary hypertension towards evaluation of innovative drugs that target vascular remodelling, rather than those with a predominantly vasodilator effect that are used for class I pulmonary artery hypertension.



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3 Hoeper MM, Halank M, Wilkens H, et al. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *Eur Respir J* 2013; **41:** 853–60.

4 Galiè N, Grimminger F, Grünig E, et al. Comparison of hemodynamic parameters in treatment-naïve and pre-treated patients with pulmonary arterial hypertension in the randomized phase III PATENT-1 study. *J Heart Lung Transplant* 2017; **36:** 509–19.

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