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Pulmonary vasodilator treatment in pulmonary hypertension due to left heart or lung disease: time for a high-definition picture?

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Dear Editor,

We read with great interest the article "Outcomes of pulmonary vasodilator use in Veterans with pulmonary hypertension associated with left heart disease and lung disease" by Gillmeyer et al.[1] Here, the authors sought to test in a real-world scenario the effect of pulmonary vasodilator therapy on patients with pulmonary hypertension (PH) due to left heart disease (Group 2 of the *6th World Symposium on Pulmonary Hypertension* classification) and PH associated with chronic lung disease (Group 3).[2] The study performed a retrospective cohort analysis and nested case control analysis of 132,552 Medicare-eligible Veterans who were attended within the Veterans Administration Healthcare (VA) system.

The study findings of increased risk of death or organ failure in patients exposed to pulmonary vasodilators are consistent with findings from randomized clinical trials[3–6] and other cohort studies and "real-world scenarios", as quoted by the authors. However, a very important lesson from over two decades of studies is that proper phenotyping of pulmonary vascular disease is key to assess risk of progression of disease. For instance, while PH is common in patients with chronic lung disease, it is usually mild to moderate.[7] A different phenotype of PH has been described in patients with chronic obstructive pulmonary disease (COPD),[8] with a predominant vascular phenotype characterized by severe hemodynamics, decreased cardiac output, and impaired ventriculo-vascular coupling, and it is been hypothesized that this subgroup of patients could benefit from pulmonary vasodilators. Vitulo et al.,[9] showed a potential benefit of sildenafil in patients with severe PH associated with COPD. The recent INCREASE study[10] (phase 3 randomized control trial of inhaled Treprostinil in patients with PH associated with interstitial lung disease) met its primary end point and demonstrated improvements in six-minute walk distance, brain natriuretic peptide (NT-proBNP), and lower risk of clinical worsening. In Group 2, vascular disease is phenotyped as isolated post-capillary PH and combined pre- and post-capillary PH, and these phenotypes have bearing on the outcomes of vasodilator treatments on these patients;[11–13] indeed, the recent HELP trial identified a subgroup of patients with post-capillary PH and heart failure with preserved ejection fraction who benefited from Levosimendan.[14] As we progress in the study of these phenotypes, both in Group 2 and Group 3 PH, we might understand which mechanisms produce these subtle but clear differences in response to vasodilator treatment.

In the study by Gillmeyer et al., given the nature of the study, data are very limited on the definitive presence of PH or its severity. It is indeed noteworthy that so many patients in the VA have been treated with pulmonary vasodilators without having been properly phenotyped with a right heart catheterization; all the more so as we know how challenging the interpretation of echocardiography can be,[15] especially in the setting of Group 2 and Group 3 PH.[7] It is thus

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difficult to glean from this data whether PH was effectively present in two-thirds of patients, let alone know its severity. It is true that in Group 2 and Group 3 PH, right heart catheterization is only recommended when the diagnosis has the potential to inform treatment (heart or lung transplantation, inclusion in a randomized controlled trial in the case of severe PH, risk factors for Group 1 or Group 4 PH), and this has been historically one of the reasons why studying these patients has been so difficult; on the other hand, in the absence of a clear treatment option, it stands to reason that this invasive procedure be restricted to the relevant cases.

We fully agree with the authors of the paper that the use of pulmonary vasodilators in Group 2 and Group 3 PH should be confined to randomized-controlled trials, not only in order to carefully monitor patients and gather data on the numerous safety concerns,[16,17] but also in order to generate new, reliable evidence on these disparate and elusive, yet deadly diseases. We also think that the use of registries will help garner more information on "real-world" scenarios and confirm on retrospective cohorts the results obtained in randomized-controlled trials, provided we are careful to study disease groups and subgroups appropriately, avoiding the temptation of lumping them together in a bigger cohort which will inevitably mixed pears with apples.

Finally, in full agreement with the recommendations for future directions in research on Group 3 PH, we call for studies that delve deeper into these heterogeneous groups of diseases. After the low-definition group photos, we believe it is time to zoom in the picture to gather a better understanding of what exactly is killing the different subgroups within Group 2 and Group 3 PH patients.

Contributions

L.P. conceived the idea; L.P. and S.S. developed it; R.J.B., D.R-C., P.V. and J.W. contributed to the manuscript; and L.P. and S.S. finalized it.

Conflict of interest

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