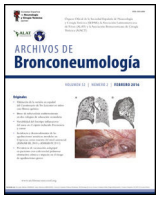
Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE
Bronconeumología

www.archbronconeumol.org



Editorial

Risk Assessment in Pulmonary Veno-Occlusive Disease: The First Step Towards Future Trials?

Pulmonary veno-occlusive disease (PVOD) represents a rare form of pulmonary arterial hypertension (PAH), distinguished by its impact on the entire pulmonary vascular bed, including pulmonary veins, capillaries, and arteries.[1] The 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines currently classify PVOD as group 1.5, titled 'PAH with features of venous/capillary involvement'.[1] PVOD is noted for its specific phenotype, reflecting venular and capillary damage, with radiological abnormalities such as septal lines, ground-glass opacities, lymph node enlargement, severe hypoxaemia, and a significantly reduced diffusing capacity for carbon monoxide (DLco).[2] PVOD can be hereditary, linked to biallelic mutations in the *EIF2AK4* gene, associated with exposure to toxic substances (e.g., alkylating agents or organic solvents), or occur sporadically.[2] The most defining characteristic of PVOD is its particularly guarded prognosis, with survival rates without transplantation around 30–35% at three years.[3] This is attributed to a limited response to PAH-approved drugs, compounded by the risk of pulmonary oedema.[3] Currently, there is a lack of data on the benefit/risk ratio of PAH-approved drugs in PVOD, which invariably is an exclusion criterion in clinical trials conducted for PAH. Thus, lung transplantation remains the standard treatment for eligible patients.[2]

In PAH, it has been clearly demonstrated that risk stratification plays a crucial role in the therapeutic approach. It enables the assessment of initial severity and guides the choice of PAH-approved drugs (mono, dual, or triple therapy), and their mode of administration, especially for treatments targeting the prostacyclin pathway (oral or parenteral).[1] Risk stratification also facilitates evaluating treatment response during follow-up and guiding treatment adjustments. In recent years, numerous risk stratification tools have been validated in large registries, notably the 4-strata and 3-strata ESC/ERS models and scores from the US REVEAL Registry.[4–7] The current treatment objective is to achieve a low mortality risk status for patients, correlating with improved outcomes. However, until recently, these risk classifications had not been applied to PVOD.

In the current issue of *Archivos de Bronconeumologia*, Cruz-Utrilla et al. have examined the relevance of risk stratification in a cohort of 54 PVOD patients from the Spanish Registry of PAH (REHAP) between 2011 and 2022.[8] First, this study corroborates the grim prognosis for these patients, with observed mortality rates of 22.9% at 3 years and 50.5% at 5 years. The authors demonstrated the prognostic efficacy of both the ESC/ERS risk score and the REVEAL Lite 2 model in PVOD at the time of diagnosis, in defining the risk of death or transplantation. These findings are consistent with a study our team conducted on a large population of 327 patients with PVOD, including baseline and follow-up assessments.[9] Indeed, Boucly et al. compared six risk assessment methods (number of four low-risk and three non-invasive low-risk variables, ESC/ERS guidelines 3-strata and 4-strata models, and REVEAL 2.0 and Lite 2 models) at baseline and early follow-up.[9] All methods were able to discriminate mortality risk, with the ESC/ERS 4-strata model proving the most accurate both at baseline and during follow-up. However, only a small fraction of PVOD patients (14%) achieved a low-risk status within a year according to the ESC/ERS 4-strata method; and contrary to PAH, the prognosis for patients achieving low- or intermediate-low-risk status at first follow-up remained poor, with 5-year survival rates of only 68% and 29%, respectively. Of note, no significant differences based on the initial PAH treatment strategy (no treatment, mono-, or dual therapy) were observed.

The question arises: What is the value of assessing the risk in a population for which no treatment has demonstrated a satisfactory benefit/risk ratio? Consequently, we cannot rely on risk stratification to guide therapeutic strategies as it is recommended for other forms of PAH. Nonetheless, these two studies have shown that prognosis can be estimated by risk stratification. This enables the optimization of timing for lung transplantation listing and prioritization of high-risk patients, who could benefit from urgent listing transplantation programmes when such options are feasible. The evaluation of risk also holds significance for PVOD in the context of future therapeutic trials. The PAH-approved drugs currently available primarily exert a pulmonary arterial vasodilatory effect, likely offering little or no impact on the capillary and venular components of PVOD and promoting pulmonary oedema. However, innovative PAH therapies targeting preferentially vascular remodelling without a major vasodilatory effect could offer promising therapeutic options for PVOD. Among these, sotatercept, targeting the activin pathway and restoring the balance of the TGF-beta pathway, demonstrated in phase 2 and 3 studies a significant effect in PAH.[10,11] Additionally, the phase 2 study with inhaled seralutinib, a small-molecule inhibitor of PDGFRα/PDGFRβ, CSF1R, and c-KIT kinase, in PAH (TORREY, NCT04456998) met its primary endpoint of reducing pulmonary vascular resistance after 24 weeks.[12] Interestingly, dysfunction in the BMPRII and PDGF pathways has been observed in human and experimental PVOD, which may justify evaluating such treatments in PVOD.[13,14]

The setting-up of clinical trials dedicated to PVOD has become an urgent goal given the severity of the disease's prognosis and the

https://doi.org/10.1016/j.arbres.2024.04.011

Please cite this article as: D. Montani, A. Boucly and O. Sitbon, Risk Assessment in Pulmonary Veno-Occlusive Disease: The First Step Towards Future Trials? Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2024.04.011

current therapeutic impasse. It is challenging to envision that the endpoints for these phase 2 studies could be directly comparable to those used for PAH, especially pulmonary vascular resistance. These recent studies[8,9] demonstrating the applicability and relevance of risk stratification in PVOD open up the possibility of using this criterion as an endpoint for future dedicated clinical trials.

Funding

None.

Conflict of interests

A. Boucly reports grants or contracts from Acceleron, AstraZeneca, Janssen and MSD, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Janssen, Merck, AOP Orphan and Ferrer, outside the submitted work; support for attending meetings and/or travel from Janssen and MSD, outside the submitted work.

O. Sitbon reports grants or contracts from Acceleron, AOP Orphan, Janssen and MSD, outside the submitted work; consulting fees from Acceleron, Altavant, Enzyvant, AOP Orphan, Ferrer, Gossamer Bio, Janssen and Merck MSD, outside the submitted work; honoraria for speaking at conferences from AOP Orphan, Janssen, Ferrer and Merck MSD, outside the submitted work; and honoraria received for Trial Steering Committee membership from Altavant, Enzyvant, Gossamer Bio and Janssen, outside the submitted work.

D. Montani reports grants or contracts from Acceleron, Janssen and Merck MSD, outside the submitted work; consulting fees from Acceleron, Janssen, Merck MSD and Ferrer, outside the submitted work; and payment or honoraria for speakers' bureaus from Bayer, Janssen, Boehringer, Chiesi, GSK, Ferrer and Merck MSD, outside the submitted work.

References

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023;61:2200879.
2. Montani D, Lau EM, Dorfmüller P, Girerd B, Jaïs X, Savale L, et al. Pulmonary veno-occlusive disease. Eur Respir J. 2016;47:1518–34.
3. Montani D, Girerd B, Jaïs X, Levy M, Amar D, Savale L, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. Lancet Respir Med. 2017;5:125–34.
4. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest. 2019;156:323–37.
5. Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL lite 2, for use in patients with pulmonary arterial hypertension. Chest. 2021;159:337–46.
6. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017;50:1700740.
7. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017;50:1700889.
8. Cruz-Utrilla A, Pérez-Olivares C, Luna-López R, Jiménez López-Guarch C, Bedate P, Martínez Meñaca A, et al. Risk stratification in pulmonary veno-occlusive disease. Arch Bronconeumol. 2024. S0300-2896(24)00051-6.
9. Boucly A, Solinas S, Beurnier A, Jaïs X, Keddache S, Eyries M, et al. Outcomes and risk assessment in pulmonary veno-occlusive disease. ERJ Open Res. 2024;10:00612–2023.
10. Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoeper MM, Preston IR, et al. Sotatercept for the treatment of pulmonary arterial hypertension. N Engl J Med. 2021;384:1204–15.
11. Hoeper MM, Badesch DB, Ghofrani HA, Gibbs JSR, Gomberg-Maitland M, McLaughlin VV, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med. 2023;388:1478–90.
12. Frantz RP, McLaughlin VV, Sahay S, Escribano Subías P, Zolty RL, Benza RL, et al. Seralutinib for the treatment of pulmonary arterial hypertension (PAH): results from the phase 2 TORREY trial. Am J Respir Crit Care Med. 2023:207. Meeting Abstracts A6726.
13. Manaud G, Nossent EJ, Lambert M, Ghigna M-R, Boët A, Vinhas M-C, et al. Comparison of human and experimental pulmonary veno-occlusive disease. Am J Respir Cell Mol Biol. 2020;63:118–31.
14. Overbeek MJ, Boonstra A, Voskuyl AE, Vonk MC, Vonk-Noordegraaf A, van Berkel MPA, et al. Platelet-derived growth factor receptor-β and epidermal growth factor receptor in pulmonary vasculature of systemic sclerosis-associated pulmonary arterial hypertension versus idiopathic pulmonary arterial hypertension and pulmonary veno-occlusive disease: a case–control study. Arthritis Res Ther. 2011;13:R61.

David Montani [a,b,c,*], Athénaïs Boucly [a,b,c], Olivier Sitbon [a,b,c]
[a] *Université Paris-Saclay, Faculté de Médecine, Le Kremlin-Bicêtre, France*
[b] *Institut National de la Santé et de la Recherche Scientifique, Unité Mixte de Recherche S_999 «Pulmonary Hypertension: Pathophysiology and Novel Therapies», Faculté de Médecine de Bicêtre et Hôpital Marie Lannelongue, Le Plessis Robinson, France*
[c] *Assistance Publique – Hôpitaux de Paris, Groupe Hospitalo-Universitaire Paris-Saclay, Hôpital Bicêtre, Département Médico-Universitaire "THORINNO", Service de Pneumologie et Soins Intensifs, Centre de Référence de l'Hypertension Pulmonaire PULMOTENSION, Le Kremlin-Bicêtre, France*

Corresponding author.
E-mail address: david.montani@aphp.fr (D. Montani)