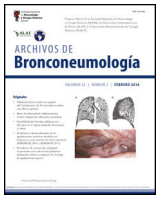
Archivos de Bronconeumología 58 (2022) 685–686

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Pulmonary Hypertension in Interstitial Lung Disease

Patients with diverse interstitial lung diseases (ILDs) may develop pulmonary hypertension (PH) during follow-up, most with a pre-capillary pattern at invasive hemodynamics, being classified within groups 3 and 5 in the current classification of PH.[1,2] Precapillary PH associated with ILD (PH-ILD) is currently defined as the presence of pulmonary vascular resistance (PVR) ≥3 WU associated with mean pulmonary arterial pressure (mPAP) >20 mmHg and pulmonary artery wedge pressure ≤15 mmHg at rest as assessed by right heart catheterization (RHC).[1,3] The majority of PH-ILD is included in the group 3 and related to the parenchymal involvement, such as observed in fibrotic idiopathic interstitial pneumonia (IIP), hypersensitivity pneumonitis and lymphangioleiomyomatosis.[1,2,4] However, PH associated with sarcoidosis, pulmonary Langerhans cell histiocytosis and metabolic disorders, given the diversity of potential pathophysiological events that might be responsible for the development of PH, are currently classified within the group 5, with unclear and/or multifactorial mechanisms.[1,2,5] Nevertheless, hypoxic vasoconstriction, remodeling of small pulmonary vessels, destruction and obliteration of the microvasculature, and upregulation of vascular modifying cytokines,[3] isolated or in combination, represent some of the recognized mechanisms potentially involved in the pathogenesis of PH-ILD.

PH determines significant morbidity and mortality in patients with ILD. Most data of PH associated with fibrotic IIP were obtained from studies with idiopathic pulmonary fibrosis (IPF), and demonstrate that the prevalence of PH increases with advanced disease. However, the development of PH in IPF is multifactorial so that the severity of PH is not always correlated with the impairment of the parenchymal involvement[2]; some patients with mild disease may present PH, which can be consistent with other groups of PH classification.[3]

Therefore, it is reasonable to screen PH in symptomatic patients with ILD. However, the most adequate method for screening PH-ILD is still unknown. Different tools may be used to screen PH in patients with parenchymal lung diseases, including peripheral oxygen saturation (SpO_2) at rest or exercise, transthoracic doppler echocardiography, six-minute walk test, diffusing capacity for carbon monoxide (DLCO), whose reduction can be compared to the decline of lung volumes, and assessment of the main pulmonary artery and aorta diameters on CT scan. These screen methods have different sensitivities according to each ILD.[3–5] RHC is the confirmatory diagnostic method of PH associated with ILD and should be considered mainly for those in which therapeutic interventions will be performed.[2,4,5] It is important to emphasize that the presence of PH in a patient with ILD does not preclude the need exclude other causes of PH, beside the parenchymal disease. In this sense, it is important to exclude the presence of left heart dysfunction and chronic thromboembolic disease. Furthermore, the main end-points to assess the response to therapeutic interventions in PH include dyspnea and quality of life scores, six-minute walking distance, decline in forced vital capacity (FVC) and in DLCO, hospitalizations, acute exacerbation, death from any cause or lung transplantation, and pulmonary hemodynamic parameters.

Several advances have been made in the approach to diseases in the area of pulmonary circulation, but consistent innovations in the treatment of PH-ILD have only occurred very recently, mostly in IIP, with a main focus in IPF.[6] Systematic reviews and randomized clinical trials with different systemic pulmonary vasoactive drugs, such as endothelin-receptor antagonists (ambrisentan and bosentan), phosphodiesterase-5 inhibitors (sildenafil) and riociguat, had conflicting results and did not demonstrate robust benefits with some of them even determining harm effects in relevant clinical, functional and pulmonary hemodynamic outcomes in patients with PH secondary to IIP. The main mechanisms speculated for the lack of positive effects of such drugs are the worsening of pulmonary ventilation/perfusion mismatch and gas exchange, and the presence of left sided heart failure.[7–11] For other ILDs, data are still scarce and less robust. A placebo-controlled trial demonstrated that bosentan improved pulmonary hemodynamics in patients with PH associated with sarcoidosis after 16 weeks, with no benefits on the distance walked.[12]

In this scenario, the use of inhaled vasodilators, such as pulse nitric oxide (NO) and treprostinil, a prostacyclin analogue, could mitigate the worsening of ventilation/perfusion mismatching through the pulmonary vasodilation of better ventilated areas.[13,14] Treatment with pulse NO for eight weeks in subjects with fibrotic ILD was safe, well tolerated, and showed improvement in physical activity and in oxygen saturation.[14] The benefit of inhaled treprostinil was demonstrated in patients with PH associated with diffuse parenchymal lung disease (INCREASE trial), with a significant improvement in the six-minute walking distance (31 m) after 16 weeks and a lower risk of clinical worsening, without increase in adverse events.[13] Additionally, a post-hoc analysis demonstrated potential favorable effects of inhaled treprostinil on FVC, mainly in those with IPF.[15]

Although the role of oxygen supplementation on PH in patients with ILD was not clearly assessed, hypoxaemia at rest, during sleep or exercise should be treated. Additionally, it is essential to optimize treatment of the parenchymal component of the underlying ILD.[2]

https://doi.org/10.1016/j.arbres.2022.02.002

However, the impact of antifibrotics on PH-ILD remains unknown. Lung transplantation, preferably bilateral, remains the unique current option with impact on survival in patients with PH-ILD.[3]

Therefore, appropriate drug treatment of PH-ILD has not been established yet. Despite the favorable perspectives with inhaled vasodilators, several questions remain unknown. It is essential to evaluate the impact of inhaled vasodilators on larger samples of patients with fibrotic ILD and on other causes of ILD, such as sarcoidosis and cystic lung diseases. Further research is warranted to address the role of inhaled vasodilators on exercise capacity, functional variables and gas exchange in the long-term, and also on mortality, need of lung transplantation and hospitalizations. The impact of combination therapy, with vasodilators and antifibrotics, in PH-ILD is unknow. It is still not determined whether inhaled vasodilators have impact not only on vascular properties, but also on parenchymal fibrosis. Furthermore, it is essential to identify the subgroups of patients, according to severity of PH and the group of ILD, that would benefit from the use of vasodilators, and to assess other treatment modalities acting on other pathways regarding the potential pathogenesis of PH-ILD, including attenuation of vascular remodeling. Due to the high complexity of the issue and to many unanswered questions, patients with PH-ILD should preferably be referred to experienced centers in PH and ILD, especially if there is a prospect of specific therapy, inclusion in clinical trials, or lung transplantation.

References

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamicdefinitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913, http://dx.doi.org/10.1183/13993003.01913-2018.
2. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015;46:903–75, http://dx.doi.org/10.1183/13993003.01032-2015.
3. Girgis RE, Hoeper MM. Pulmonary hypertension in fibrosing idiopathic interstitial pneumonia: uncertainties, challenges and opportunities. J Heart Lung Transplant. 2021;40:872–81, http://dx.doi.org/10.1016/j.healun.2021.03.004.
4. Freitas CSG, Baldi BG, Jardim C, Araujo MS, Sobral JB, Heiden GI, et al. Pulmonary hypertension in lymphangioleiomyomatosis: prevalence, severity and the role of carbon monoxide capacity as a screening method. Orphanet J Rare Dis. 2017;12:74, http://dx.doi.org/10.1186/s13023-017-0626-0.
5. Heiden GI, Sobral JB, Freitas CSG, Albuquerque ALP, Salge JM, Kairalla RA, et al. Mechanisms of exercise limitation and prevalence of pulmonary hypertension in pulmonary Langerhans cell histiocytosis. Chest. 2020;158:2440–8, http://dx.doi.org/10.1016/j.chest.2020.05.609.
6. Ota-Arakaki JS, Campos FTAF, Souza R. World Pulmonary Hypertension Day: reflections and planning. J Bras Pneumol. 2021;47:e20210251, http://dx.doi.org/10.36416/1806-3756/e20210251.
7. Baddini-Martinez J, Ferreira J, Tanni S, Alves LR, Cabral Junior BF, Carvalho CRR, et al. Brazilian guidelines for the pharmacological treatment of idiopathic pulmonary fibrosis Official document of the Brazilian Thoracic Association based on the GRADE methodology. J Bras Pneumol. 2020;46:e20190423, http://dx.doi.org/10.36416/1806-3756/e20190423.
8. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, et al. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2014;190:208–17, http://dx.doi.org/10.1164/rccm.201403-0446OC.
9. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013;158:641–9, http://dx.doi.org/10.7326/0003-4819-158-9-201305070-00003.
10. Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MH, Martinez FM, et al. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP: a randomised, placebo-controlled phase 2b study. Lancet Respir Med. 2019;7:780–90, http://dx.doi.org/10.1016/S2213-2600(19)30250-4.
11. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med. 2010;363:620–8, http://dx.doi.org/10.1056/NEJMoa1002110.
12. Baughman RP, Culver DA, Cordova FC, Padilla M, Gibson KF, Lower EE, et al. Bosentan for sarcoidosis-associated pulmonary hypertension: a double-blind placebo controlled randomized trial. Chest. 2014;145:810–7, http://dx.doi.org/10.1378/chest.13-1766.
13. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021;384:325–34, http://dx.doi.org/10.1056/NEJMoa2008470.
14. Nathan SD, Flaherty KR, Glassberg MK, Raghu G, Swigris J, Alvarez R, et al. A randomized, double-blind, placebo-controlled study of pulsed, inhaled nitric oxide in subjects at risk of pulmonary hypertension associated with pulmonary fibrosis. Chest. 2020;158:637–45, http://dx.doi.org/10.1016/j.chest.2020.02.016.
15. Nathan SD, Waxman A, Rajagopal S, Case A, Johri S, DuBrock H, et al. Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonar hypertension: a post-hoc analysis of the INCREASE study. Lancet Respir Med. 2021;9:1266–74, http://dx.doi.org/10.1016/S2213-2600(21)00165-X.

Bruno Guedes Baldi[a,b,*], Rogério Souza[a]

[a] *Divisão de Pneumologia, Instituto do Coração (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil*

[b] *Hospital do Coração, São Paulo, Brazil*

Corresponding author.

E-mail address: bruno.baldi@hc.fm.usp.br (B.G. Baldi).