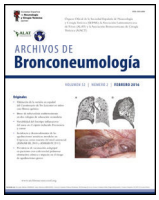
Arch Bronconeumol. 2017;53(5):235–236

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Novelties in the Treatment of Pulmonary Hypertension

Novedades en el tratamiento de la hipertensión pulmonar

Jason Weatherald[a,b,c,d], Yu Taniguchi[a,b,c,e], Marc Humbert[a,b,c,*]

[a] Faculté de Médecine, Université Paris-Sud, Université Paris-Saclay, Le Kremlin-Bicêtre, France
[b] Service de Pneumologie, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France
[c] INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis Robinson, France
[d] Department of Medicine, Division of Respirology, University of Calgary, Calgary, Canada
[e] Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are progressive diseases of the pulmonary circulation that lead to right heart failure. Exciting recent advances have improved prognosis, however PAH and CTEPH remain disabling and life limiting conditions.

Currently approved medical therapies improve functional capacity, hemodynamics and delay clinical worsening by targeting the 3 main pathobiologic pathways: prostacyclin, endothelin, and nitric oxide. Recently, several new agents targeting the classic PAH pathways have been developed for the treatment of pulmonary hypertension. However, a targeted treatment that delays or reverses vascular remodeling remains elusive. Recent attempts to specifically inhibit or reverse vascular proliferation in PAH with imatinib, a tyrosine kinase inhibitor, were disappointing because of the high dropout rate due to adverse events (over 30%) and the high incidence of subdural hematoma.[1]

Selexipag is a new oral selective PGI2 receptor agonist that targets the prostacyclin pathway. In the placebo-controlled GRIPHON study of 1156 patients with PAH, selexipag reduced the risk of death or PAH-related complications by 40%, an effect that was primarily driven by a reduction in disease progression and hospitalization for PAH; mortality was similar in both study groups.[2] Importantly though, the treatment effect was consistent across treatment naïve patients and those receiving background phosphodiesterase type 5 (PDE5) inhibitors and/or endothelin receptor antagonists. Unlike PDE5 inhibitors, riociguat acts by directly stimulating soluble guanylate cyclase, independent of nitric oxide availability. In recently published long-term extension studies of randomized controlled trials of PAH patients (PATENT-2)[3] and CTEPH patients (CHEST-2),[4] riociguat was well tolerated with sustained improvements in functional capacity and 6-minute walk distance in both patient populations. Riociguat is also the only targeted medication currently approved for treating CTEPH.

Combination therapy in PAH has gained momentum, however there remains some debate on the optimal strategy: upfront versus sequential addition of therapies. The COMPASS-2 study evaluated a strategy of sequentially adding bosentan to patients on background sildenafil for at least 12 weeks.[5] This was a negative study with regards to the primary endpoint; however, a long recruitment period and high dropout rate resulted in the study being underpowered. In contrast, the AMBITION trial evaluated an upfront combination approach using ambrisentan and tadalafil versus monotherapy in treatment naïve patients.[6] There was a 50% reduction in the primary endpoint with initial combination therapy, driven by a reduction in hospitalization for PAH. Based on the results of AMBITION, initial combination therapy with ambrisentan and tadalafil was given a class IB recommendation in the recent European guidelines.[7] This recommendation is supported by a recent analysis from the French registry showing a 3-year survival of 84% in patients treated with initial dual oral combination therapy compared to an expected historical 3-year survival of 66%.[8]

Although pulmonary endarterectomy remains the gold standard treatment for eligible CTEPH patients, many are not eligible for surgery due to inaccessible distal thromboembolic disease or comorbidities. Balloon pulmonary angioplasty (BPA), an endovascular procedure to widen narrowed or obstructed pulmonary arteries, has emerged as an exciting alternative treatment option for patients with non-operable CTEPH or patients with persistent pulmonary hypertension after endarterectomy. The first series published in 2001 demonstrated a reduction in mean pulmonary artery pressure (mPAP) of 9 mmHg, but reported a 5.6% rate of in-hospital death. Following refinements in the technique, several reports, mainly from Japan, now support the efficacy and safety of BPA. The hemodynamic benefits were summarized in a recent review article, which reported an overall reduction in mPAP of 12–21 mmHg from baseline, and a mortality rate of 0.0–3.4% after 2–5 angioplasty sessions.[9] A recent Japanese study reported the

* Corresponding author.
E-mail address: marc.humbert@aphp.fr (M. Humbert).

http://dx.doi.org/10.1016/j.arbres.2017.01.016

results of 170 patients who underwent BPA over a 7 year period. They found sustained hemodynamic improvements, almost to within the normal range, in mPAP and pulmonary vascular resistance up to 3.5 years after BPA.[10] In this series, the 1, 3, and 5-year survival rates were 98.7%, 98.0%, and 95.5%, however 1 death was attributed to multi-organ failure secondary to pulmonary artery injury, a known complication of BPA. Severe and fatal complications, including reperfusion edema or pulmonary artery perforation, may be minimized as the learning curve progresses. Although the indications and limitations have not been fully established, BPA has the potential to become a key treatment strategy for patients with non-operable CTEPH. An open-label, randomized controlled trial comparing BPA to riociguat in non-operable CTEPH patients is currently underway in France, with a primary endpoint of change in pulmonary vascular resistance at 26 weeks (RACE trial, NCT02634203). This trial may help clarify the relative place of BPA and riociguat in a CTEPH treatment algorithm.

In conclusion, there have been important advances in the treatment of PAH and CTEPH over the past few years. However, PAH remains a progressive and fatal disease in most cases. Until the development of effective therapies that can slow or reverse vascular proliferation, inflammation and remodeling, parenteral prostanoids, combination therapy and lung transplantation are the only life-prolonging therapies. Patients with CTEPH now benefit from several therapeutic options including possible combinations of surgery, medical therapy and BPA. Riociguat and balloon pulmonary angioplasty are new effective options for CTEPH that result in significant clinical improvements for non-operable patients and those with persistent pulmonary hypertension after endarterectomy.

Conflict of interests

Dr. Humbert reports personal fees from Actelion Pharmaceuticals Ltd., grants and personal fees from Bayer, grants and personal fees from GSK, personal fees from Pfizer; and personal fees from Novartis, outside the submitted work. Dr. Weatherald has received grants from the European Respiratory Society and Canadian Thoracic Society; personal fees and non-financial support from Actelion and Bayer, outside the submitted work. Dr. Taniguchi has no conflict of interest to declare.

Acknowledgements

Dr. Jason Weatherald is the recipient of a joint ERS/CTS Fellowship (LTRF 2015-4780).

References

1. Frost AE, Barst RJ, Hoeper MM, Chang H-J, Frantz RP, Fukumoto Y, et al. Long-term safety and efficacy of imatinib in pulmonary arterial hypertension. J Heart Lung Transplant. 2015;34:1366–75.
2. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373:2522–33.
3. Rubin LJ, Galie N, Grimminger F, Grünig E, Humbert M, Jing Z-C, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). Eur Respir J. 2015;45:1303–13.
4. Simonneau G, D'Armini AM, Ghofrani H-A, Grimminger F, Hoeper MM, Jansa P, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur Respir J. 2015;45:1293–302.
5. McLaughlin V, Channick RN, Ghofrani H-A, Lemarié J-C, Naeije R, Packer M, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. Eur Respir J. 2015;46:405–13.
6. Galie N, Barberà JA, Frost AE, Ghofrani H-A, Hoeper MM, McLaughlin VV, et al., AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015;373:834–44.
7. Galie N, Humbert M, Vachiéry J-L, 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.
8. Sitbon O, Sattler C, Bertoletti L, Savale L, Cottin V, Jaïs X, et al. Initial dual oral combination therapy in pulmonary arterial hypertension. Eur Respir J. 2016;47:1727–36.
9. Satoh T, Kataoka M, Inami T, Ishiguro H, Yanagisawa R, Shimura N, et al. Endovascular treatment for chronic pulmonary hypertension: a focus on angioplasty for chronic thromboembolic pulmonary hypertension. Expert Rev Cardiovasc Ther. 2016;14:1089–94.
10. Inami T, Kataoka M, Yanagisawa R, Ishiguro H, Shimura N, Fukuda K, et al. Long-term outcomes after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Circulation. 2016;134:2030–2.