



# New horizons in pulmonary arterial hypertension management

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Developments in the management of pulmonary arterial hypertension <http://ow.ly/BBeqe>

Significant developments have been made in the management of pulmonary arterial hypertension (PAH) over the past year. These include an increased understanding of the need for earlier detection and treatment, changing disease characteristics, the continuing development of new treatment options and an increasing perception of the specific challenges that patients with PAH face at each stage of illness. Notably, an updated treatment algorithm from the 5th World Symposium on Pulmonary Hypertension has been published [1], reflecting recent changes in available evidence. The articles in this issue of the *European Respiratory Review* encompass the breadth of these issues and are based on presentations from the 13th International Pulmonary Hypertension Forum held in April 2014 in Lisbon, Portugal. These articles not only provide a snapshot of the current understanding but also offer a forward-looking view to new horizons in PAH management.

Progressive failure of the right ventricle due to increased pulmonary vascular resistance is a significant cause of morbidity and mortality in patients with PAH. In the article by NAEIJE and MANES [2], the measurement and pathobiology of the interaction between the right ventricle and the arterial system, the role of diastolic function, and the influence of the left ventricle function on right ventricular activity are discussed.

In examining the clinical and disease characteristics of patients living with PAH, the historical importance of registry data cannot be overstated. As the body of evidence from registries continues to build, it offers a window into changes in patient populations and characteristics over time. In the article by HOEPER and GIBBS [3], new trends in PAH demographics and patient subsets, the reasons for these changes, and the potential implications for disease management are identified.

Children with PAH are another distinct subset of patients requiring a tailored approach to diagnosis and treatment [4, 5]. Treatment of PAH in children is particularly challenging due to difficulties of evaluating treatment efficacy in appropriately designed clinical trials and the limited evidence currently available for PAH drugs in this population. In the article by BEGHETTI and BERGER [6], these challenges are discussed in the context of current options for disease classification, available data from registries and clinical trials, and the authors' own clinical experience.

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While historically, combination therapy has been widely used in PAH management, support for this use has been primarily based on expert opinion, registry data or prior clinical experience. However, as evidence from clinical trials and real-world data increase, it provides a new context in which the role and importance of combination therapy must be re-evaluated. A recent example of this change is reflected in the change in recommendation grade for sequential combination therapy in the updated treatment algorithm [1], which is a result of trials such as SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) [7] and PATENT-1 (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1) [8]. The article by GHOFRANI and HUMBERT [9] offers a comprehensive summary of the latest available data in combination therapy, and the resultant insights and implications for current and future treatment.

The use of upfront combination therapy is now recommended in patients who are in World Health Organization functional class III/IV, albeit with a lower level of recommendation than monotherapy and sequential combination therapy [1]. A recent pilot study showed promise in a small group of patients with severe PAH [10, 11]. This treatment approach, and the multifaceted reality of treating severe PAH, is the focus of a case-based review by SITBON [12], which charts the progress of a patient with severe PAH associated with mixed connective tissue disease who received upfront triple combination therapy for PAH along with immunosuppressive therapy.

The successful treatment of patients with severe PAH requires both timely treatment changes (in the form of transitioning to intravenous or subcutaneous pharmacotherapy in response to disease worsening) and managing the transition, when necessary, to lung transplantation. This requires knowledge of the treatments available to patients with severe PAH, an understanding of the level of clinical assessment and examination required, and an awareness of the techniques that can be employed to bridge patients to transplantation. The article by CORRIS and DEGANO [13] offers an excellent summary of these elements.

The need to consider transplantation highlights how the long-term prognosis for patients with this disease remains poor, in spite of continued advances in treatment options [14]. In this context, the expectations placed on treatment by physicians and patients may differ. What constitutes treatment success for the patient? And does this expectation match that of the treating physician? What level of patient support is required beyond diagnosis and pharmacotherapy? HOWARD *et al.* [15] discuss these questions from both a physician and patient perspective, offering a unique insight into the essential requirements for improved patient support and decision making.

Together, the articles in this issue of *European Respiratory Review* highlight the multifaceted nature of PAH and the progress that has been made in managing this difficult disease, through registries and randomised controlled trials. These articles also highlight the importance that the exchange and communication of ideas amongst physicians and patients can play in recognising and moving towards new horizons in PAH treatment.

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### References

- 1 Galiè N, Corris PA, Frost A, *et al.* Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D60–D72.
- 2 Naeije R, Manes A. The right ventricle in pulmonary arterial hypertension. *Eur Respir Rev* 2014; 23: 476–487.
- 3 Hoeper MM, Gibbs JSR. The changing landscape of pulmonary arterial hypertension and implications for patient care. *Eur Respir Rev* 2014; 23: 450–457.
- 4 Ivy DD, Abman SH, Barst RJ, *et al.* Pediatric pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D117–D126.
- 5 Berger RM. Pulmonary hypertension: smaller kids, smaller steps. *Lancet Respir Med* 2014; 2: 348–350.
- 6 Beghetti M, Berger RMF. The challenges in paediatric pulmonary arterial hypertension. *Eur Respir Rev* 2014; 23: 498–504.
- 7 Pulido T, Adzerikho I, Channick RN, *et al.* Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809–818.
- 8 Ghofrani HA, Galiè N, Grimminger F, *et al.* Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 330–340.
- 9 Ghofrani H-A, Humbert M. The role of combination therapy in managing pulmonary arterial hypertension. *Eur Respir Rev* 2014; 23: 469–475.
- 10 Sitbon O, Jais X, Savale L, *et al.* Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J* 2014; 43: 1691–1697.
- 11 McGoan MD. Upfront triple therapy for pulmonary arterial hypertension: is three a crowd or critical mass? *Eur Respir J* 2014; 43: 1556–1559.
- 12 Sitbon O, Bertoletti L. Connective tissue disease associated with pulmonary arterial hypertension: management of a patient with severe haemodynamic impairment. *Eur Respir Rev* 2014; 23: 505–509.
- 13 Corris P, Degano B. Severe pulmonary arterial hypertension: treatment options and the bridge to transplantation. *Eur Respir Rev* 2014; 23: 488–497.
- 14 Barst RJ, Chung L, Zamanian RT, *et al.* Functional class improvement and 3-year survival outcomes in patients with pulmonary arterial hypertension in the REVEAL Registry. *Chest* 2013; 144: 160–168.
- 15 Howard LS, Ferrari P, Mehta S. Physicians' and patients' expectations of therapies for pulmonary arterial hypertension: where do they meet? *Eur Respir Rev* 2014; 23: 458–468.