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EDITORIAL

Pulmonary arterial hypertension: bridging the present to the future

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The past decade has witnessed extensive progress in basic and clinical research in the field of pulmonary hypertension (PH), a group of chronic conditions characterised by high pressure in the pulmonary circulation. National and international PH registries have achieved much to advance our understanding of the epidemiology, demographics, aetiology, clinical course, haemodynamics, disease management and treatment outcomes of PH [1–7]. Therapies available to target the pathology of pulmonary arterial hypertension (PAH) have expanded considerably and more options are expected in the near future [8, 9]. Although this progress has steadily improved the outlook for PAH patients, there remains a need for further developments to ensure that advances continue to be made.

The articles and case reports in this issue of the *European Respiratory Review* discuss key and current issues in the management of patients with PH. The authors, all experts in the field of PH, delivered the presentations upon which the articles are based at the 11th International Pulmonary Hypertension Forum in Dublin, Ireland on May 12–13, 2012. This annual platform for the exchange of knowledge and experience among clinicians and researchers was attended by over 1,000 healthcare professionals from all over the world, highlighting the continuing interest in this devastating group of diseases.

The European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines provide a clear classification of the major clinical subcategories of PH [10, 11], based on shared pathophysiological mechanisms, similar clinical presentations and therapeutic approaches [12]. It is Group 1 PH, namely PAH, that has been subject to the most rapid advancement in terms of knowledge and treatment options in the past decade. Because this group of patients is treatable, accurate and prompt diagnosis are particularly critical; PAH patients receiving treatment in World Health Organization functional class (WHO-FC) I/II have a better prognosis than those in WHO-FC III/IV. This applies across a broad range of PAH aetiologies [3, 4, 13, 14].

As highlighted by VACHIÉRY and GAINE [15], management of patients with PAH remains challenging at all stages, including initial diagnosis. Studies, such as the EARLY (Endothelin Antagonist Trial in Mildly Symptomatic PAH patients) study [16], demonstrate that PAH is a rapidly progressing disease, even in patients with mild symptoms, underlining the need for prompt diagnosis and intervention. However, early diagnosis is confounded by the subtle, nonspecific nature of symptoms and by the low prevalence of PAH. This means that there is a low level of suspicion among clinicians who must first rule out more common conditions such as asthma, chronic obstructive pulmonary disease, chronic heart failure, anaemia and other forms of PH before arriving at a diagnosis of PAH, often >2 yrs after initial presentation [5]. As a consequence, 70–80% of PAH patients are diagnosed in WHO-FC III/IV, a proportion that has not changed substantially since the 1980s [17].

PAH is, however, being diagnosed earlier in some patients. The recognised risk of developing PAH in patients with systemic sclerosis (SSc) has led to the implementation of successful screening programmes within the past decade. Adoption of a systematic echocardiography-based screening programme has resulted in much earlier diagnosis of PAH in SSc patients compared with those identified in routine clinical practice [18]. Importantly, the 8-yr survival estimate among SSc-PAH patients diagnosed through the screening programme (64%) was significantly higher than that among patients diagnosed in routine practice (17%).

As pointed out by HUMBERT *et al.* [19], despite updated guidance and advances in treatment, the long-term prognosis for patients with PAH remains poor. It is essential that every effort continues to be made in promoting early detection of PAH so that appropriate management can be offered without undue delay. Doppler echocardiography-based screening programmes, however, do have limitations. The accuracy of Doppler echocardiography is heavily influenced by the skill of the echocardiographic operator and the subsequent interpretation of the data by the clinician and may not be as reliable a method for detecting asymptomatic/early PAH as it is for identifying more advanced disease. The limitations of echocardiography for detecting PAH in asymptomatic patients are reflected by a change in the ESC/ERS guidelines [10, 11] and emphasise the need for alternative approaches to improve the selection of patients for referral to diagnostic right heart

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catheterisation (RHC). In their article, HUMBERT *et al.* [19] highlight the DETECT study (Clinicaltrials.gov NCT00706082) as being the first prospective study to have systematically evaluated the accuracy of several potential screening tests for the early detection of PAH in SSc. The challenge with all screening tools is to strike the right balance between specificity and sensitivity. In the case of PAH, achieving the right balance between the number of RHC referrals and an acceptable level of missed PAH diagnoses is a clinical, and possibly financial, dilemma for all those involved. However, whichever screening approach is adopted, it is unlikely that performance will be consistent across patient populations with PAH due to different aetiologies.

PAH is a recognised complication of congenital heart disease (CHD). The development of PAH in patients with CHD (PAH-CHD) is associated with increased morbidity and mortality and is particularly prevalent in patients with uncorrected systemic-to-pulmonary intra-cardiac shunts. Pulmonary pressures can elevate to such an extent that the shunt is reversed, resulting in the return of deoxygenated blood to the systemic circulation and the development of Eisenmenger's syndrome, the most advanced form of PAH-CHD. The article by D'ALTO and MAHADEVAN [20] gives an overview of the demographics, pathophysiology and treatment of PAH-CHD and focuses on individuals with Down's syndrome as an important and challenging patient group.

The key challenge in managing patients with PAH-CHD is the heterogeneous nature of the population. This is exemplified in the case study from DANIELS [21], which highlights a number of important issues around the management of adults with PAH-CHD, including: the benefit of undergoing corrective surgery within the first 12 months of life to limit the potential sequelae of CHD [22]; the association between lesion repair in the presence of established PAH and acceleration of disease progression [22]; the timing of lesion repair with respect to the degree of systemic-to-pulmonary shunting [23, 24]; the clinical and survival benefits of PAH-specific therapy in Eisenmenger's syndrome [14, 25]; and loss to follow-up.

Management strategies for PAH have evolved dramatically in recent years. In clinical practice, a goal-oriented approach to therapy is followed by many centres. Although recommended in the current ESC/ERS guidelines [10, 11], this approach has only been evaluated in a single-centre study in which idiopathic PAH patients receiving PAH-specific therapies had better outcomes than historical controls [26]. Although there is evidence that patients reaching certain targets during treatment have an improved long-term outcome [27–31], the clinically relevant target most likely to optimise patient outcomes remains unknown. Work continues to be conducted to develop new, more advanced treatments to improve the prospects of patients with PAH. All the therapeutic options currently available to clinicians target one of three key pathological pathways in PAH: the endothelin, nitric oxide and prostacyclin pathways. In their article, SITBON and MORRELL [32] describe how further advances in the understanding of these mechanisms has resulted in the development of a number of novel therapeutic options, including macitentan, riociguat and selexipag.

A greater understanding of the endothelial system has provided the rationale for developing macitentan, a dual endothelin receptor antagonist with enhanced tissue penetration designed to optimise efficacy. Pre-clinical data suggest that macitentan has improved efficacy and favourable binding kinetics compared with both bosentan and ambrisentan [33–35]. The results from the recently completed landmark phase III SERAPHIN study (Study with endothelin receptor antagonist in pulmonary arterial hypertension to improve clinical outcome; Clinicaltrials.gov NCT00660179) are eagerly awaited. SERAPHIN was an event-driven study whose primary endpoint was time to first morbidity or mortality event. To date, it is the largest prospective, controlled study in PAH. Drugs targeting the nitric oxide pathway in a different way to the phosphodiesterase type-5 inhibitors, sildenafil and tadalafil, are also in development. For example, riociguat stimulates soluble guanylate cyclase directly, increasing sensitivity to low levels of nitric oxide [36] and phase III randomised controlled trials are now complete. Drugs targeting the prostacyclin pathway have always had limitations; inconvenient modes of administration, short half-lives and nonspecific receptor interactions. Clinical trials with two oral prostacyclin analogues, treprostinil and beraprost, have had mixed results. Promising proof-of-concept clinical trial results, however, have been obtained with the first-in-class, selective prostacyclin receptor agonist, selexipag. Selexipag has been shown to significantly lower pulmonary vascular resistance and improve exercise capacity. Further investigation of selexipag is ongoing in the double-blind, randomised, placebo-controlled, phase III GRIPHON study (Prostacyclin receptor agonist in pulmonary arterial hypertension; Clinicaltrials.gov NCT01106014).

As well as the three established pathophysiology pathways, targeting the platelet-derived growth factor pathway with tyrosine kinase inhibitors, such as imatinib, and the serotonin pathway with antagonists, such as terguride, may represent novel pharmacological strategies in PAH [9, 37]. With so much effort and activity in this field, it is hoped that, in the not too distant future, new treatment(s) will be available that will improve the prognosis for patients with PAH.

Although PAH is the most studied form of PH, the increasing incidence of systemic hypertension and ischaemic heart disease, now the most common causes of PH due to left heart disease (PH-LHD; Group 2 PH), together with the increasing number of patients presenting with PH, mean that LHD represents the most frequent cause of PH. In their article, GUAZZI and GALIÈ [38] give an overview of the pathophysiology and epidemiology of PH-LHD and discuss the challenges associated with its management and treatment. A key issue is the need for careful patient evaluation; according to the ESC/ERS guidelines, PH-LHD is distinguished from PAH by the presence of a pulmonary capillary wedge pressure (P_{pcw}) >15 mmHg. P_{pcw} is widely assumed to be a surrogate marker for left ventricular end diastolic pressure (LVEDP), but in a large study including over 4,000 patients with PH, reliance on P_{pcw} rather than LVEDP may have resulted in misdiagnosis in around half of the patients [39]. The development of PH-LHD is associated with particularly poor prognosis, but despite this and the size of the Group 2 PH population, management options for these patients are limited. In stark contrast to the strides made in the management of patients with PAH, there are still virtually no treatment options for patients with PH-LHD. Guidelines limit advice to management of systemic

hypertension and volume status and to optimisation of underlying conditions. The lack of recommendations concerning the use of PAH-specific therapies in patients with PH-LHD reflects the current dearth of data. To date, most therapeutic strategies aimed at PAH have not shown positive results in patients with PH-LHD, although recent results with phosphodiesterase type-5 inhibitors have been more encouraging. There is a pressing need for more research into the underlying mechanisms of PH-LHD and new therapeutic options to help drive the development of treatment guidelines for this neglected patient group.

The articles in this issue of the *European Respiratory Review* indicate the ongoing commitment of basic scientists and clinical researchers into the management of PAH. However, they also serve as a reminder that progress is not evident in all areas. Further research is required to improve the lives of patients with all forms of PH, particularly the majority with PH-LHD.

STATEMENT OF INTEREST

M. Humbert has relationships with drug companies including Actelion, Aires, AstraZeneca, Bayer, Bristol-Myers Squibb, GSK, Merck, Novartis, Nycomed, Pfizer, Stallergènes, TEVA and United Therapeutics. In addition to being an investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. R. Souza has received lecture fees from Actelion, Bayer, GSK and Lilly, and has participated in advisory boards from Actelion, Bayer, Lilly and GSK. N. Galiè served as a consultant and received payment for lecture fees from Actelion Pharmaceuticals Ltd, Pfizer, GSK, Eli Lilly and Bayer Schering Pharma. V. McLaughlin has received speaking and/or consulting fees from Actelion, Bayer, Gilead and United Therapeutics. The University of Michigan has received research funding for multicentre trials from Actelion, Novartis, Pfizer and United Therapeutics. G. Simonneau has relationships with pharmaceutical companies including Actelion, Bayer HealthCare, Eli Lilly, GSK, Novartis and Pfizer. In addition to being an investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. L. Rubin has received consulting fees from Actelion, United Therapeutics, Bayer, GSK, Pfizer, Aires, GeNO and Gilead, and has served as an expert witness in litigation dealing with PAH.

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