



EDITORIAL

A decade of achievement in pulmonary hypertension

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The past decade has witnessed unprecedented change in the field of pulmonary hypertension (PH). PH has previously been called an orphan disease; that is, a condition that affects few individuals and is overlooked by the medical profession and pharmaceutical companies [1]. Although undoubtedly rare, the concept that PH is “overlooked” cannot be considered to be the case today. In recent years there have been a number of important publications in the field that have significantly improved our understanding of PH, helped guide patient management and laid foundations for future research [2]. The articles in this issue of the *European Respiratory Review* aim to discuss such contemporary issues in PH. The authors, all experts in the field of PH, delivered the presentations upon which the papers are based at two international meetings sponsored by Actelion Pharmaceuticals (Allschwil, Switzerland). These meetings – the Fourth International Systemic Sclerosis Forum, Barcelona, Spain, February 5–6, 2011 and the Tenth International Pulmonary Hypertension Forum, Munich, Germany, March 26–27, 2011 – were each attended by over 1,000 healthcare professionals from all over the world, thus emphasising the increasing global interest in this devastating disease.

The clinical classification of PH has evolved since the initial proposal at the first international conference on primary PH in 1973 [3]. Two updates, one from the Second and Third World Symposia on Pulmonary Hypertension in Evian, France, 1998 and Venice, Italy, 2004 [4], and the other from the Fourth World Symposium on Pulmonary Hypertension in Dana Point, CA, USA, 2008 [5] have been published in the past 10 yrs. The more recent set of guidelines, based on the proceedings from Dana Point [5, 6], have been jointly published by the European Society of Cardiology (ESC) and European Respiratory Society (ERS) and endorsed by the International Society for Heart and Lung Transplantation [7, 8]. These guidelines give a robust haemodynamic definition of PH as an increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest, as assessed by right heart catheterisation. These guidelines also provide very clear classifications of the five major clinical subcategories of PH. It is group 1 PH, namely pulmonary arterial hypertension (PAH),

that has been subject to the most rapid advancement in terms of knowledge and treatment options in the past decade.

Early symptoms of PH, and PAH in particular, are not specific and include dyspnoea, fatigue, weakness and syncope. Much progress has been made in the identification of patients with suspected PH. Diagnostic algorithms and procedures have been refined over the years and guidelines now give clear recommendations on how to identify and distinguish between the different clinical groups [7, 8]. The diagnosis of PAH is one of exclusion of all other PH conditions. Accurate and prompt diagnosis of PAH is especially important, as PAH is a treatable condition, and earlier intervention when the disease is less established may be associated with better outcome [9–11]. PAH has several known causes, including genetic mutations and toxins, and is also known to be associated with conditions such as congenital heart disease and connective tissue disease. The knowledge that patients with systemic sclerosis are at risk of developing PAH has led to the implementation of highly successful screening programmes within the past decade [11]. In their review, DENTON and HACHULLA [12] discuss the identification of risk factors for the development of PAH in patients with systemic sclerosis and the impact this would have for screening in the future.

One of the truly remarkable achievements in PH has been the number and extent of national and international PH registries that have been established over the past 10 yrs. Registries such as REVEAL (Registry to Evaluate Early And Long-term pulmonary arterial hypertension disease management) and the French ItinérAIR PAH registry have done much to advance our understanding of the epidemiology, demographics, aetiology, clinical course, haemodynamics, disease management and treatment outcomes of PAH [13–17]. These registries provide a rich source of data and will continue to inform on the management of PAH in years to come [2, 18].

In addition to a better understanding of the natural history and clinical consequences of PAH, the pathophysiology of the disease has also been more fully elucidated over the past decade. A greater understanding of aberrations in the signalling pathways that lead to the characteristic vasculopathy of PAH has led to the development of targeted PAH therapies. From just one intravenous drug, epoprostenol, which became widely available in the 1990s, four oral therapies (bosentan, ambrisentan, sildenafil and tadalafil) are now available, as well as several other parenteral prostanoids [19]. As described by McLAUGHLIN [20], we can expect to see further progression and achievements in therapeutics over the next decade, with new improved agents in established drug classes, such as macitentan; new classes acting on established pathways, such as

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selexipag and riociguat; and new drugs aimed at new pathways, such as imatinib [19].

The availability of different classes of drugs has enabled the evolution of treatment algorithms such as the one described in the ESC/ERS guidelines [7, 8]. Perhaps the greatest change in the recent past in this respect has been a move away from a treatment paradigm in which therapy is only escalated when the patient shows signs of deterioration, to one of goal-oriented therapy [21]. As described by SITBON and GALIÈ [22] in a previous issue of the *European Respiratory Review*, goal-oriented therapy is a strategy that uses prognostic indicators of survival as treatment targets. For example, across PAH aetiologies, patients in World Health Organization functional class (WHO FC) II have been shown to have better survival rates than those in WHO FC III/IV [22]. Therefore, setting WHO FC II as a treatment goal makes sense. So, instead of being satisfied when a patient is stabilised in WHO FC III, therapy would be escalated until symptoms are improved to the extent that the patient is in WHO FC II. Of course this is a simplistic example and, in reality, a range of clinical parameters are used to regularly assess patients' response to treatment and determine the next steps [7, 8]. Moreover, treatment goals need to take into account patient factors such as age, weight and comorbidities, and also disease aetiology. At present, treatment steps for goal-oriented therapy include escalating from monotherapy to sequential combination therapy [7, 8]. The use of combination therapy and the evolution of patient management in recent years are nicely demonstrated in a case report by GATZOULIS [23]. In addition, preliminary evidence described by SITBON and SIMONNEAU [24] in this issue of the *European Respiratory Review* indicates that a future treatment trend may be upfront double or triple combination therapy, especially for patients in the severe stage of the disease who represent a particularly challenging population.

The use of prognostic indicators to direct treatment represents a real advance in PAH disease management, and a number of surrogate markers have been investigated that are commonly used to assess patients and monitor treatment response. As many of these markers reflect different features of the pathophysiology of PAH, their combination would be expected to provide a more comprehensive and accurate assessment of patient status and prognosis. This approach is recommended in treatment guidelines [7, 8] and the concept of integrated evaluation has been emphasised in recent studies [25]. In his paper on prognostic indicators in PAH, HOWARD [26] discusses the clinical parameters recommended as treatment goals in the ESC/ERS guidelines [7, 8] and explains their link to a previously underappreciated aspect of PAH, namely that they reflect right ventricular function. As outlined by HOWARD [26] and further discussed by VONK NOORDEGRAAF and GALIÈ [27], it is the response of the right ventricle to an increased afterload (resulting from increasingly high pulmonary arterial pressure), which is the greatest determinant of a patient's symptoms and survival. Indeed, despite being primarily a disease of the pulmonary vasculature, it is right heart failure that is the major cause of death in patients with PAH. On this theme, GUPTA *et al.* [28] explored the use of tools that measure right heart function, such as right heart catheterisation, echocardiography and cardiac magnetic resonance in the diagnosis, evaluation and prognosis of PAH.

The achievements in therapeutics and the evolution of management strategies for PAH have led to an improvement in survival in the modern treatment era [11, 15]. Although we are still a long way from finding a cure for PAH, it is without doubt that PAH patients in the modern treatment era are less functionally impaired and live for longer. However, a certain proportion of patients fail to respond adequately to medical therapy and surgical intervention, either balloon atrial septostomy or lung transplantation, is necessary. In his report, HOEPER [29] describes the case of a young female with idiopathic PAH who, despite an initially good response to monotherapy and then sequential combination therapy, rapidly deteriorated. She developed right heart failure with renal failure and lactic acidosis within 48 h of hospital admission and her only hope was lung transplantation. The patient was kept alive on veno-arterial extracorporeal membrane oxygenation, and was conscious and without ventilation for 42 days until suitable donor organs became available. She is now doing well after successful bilateral lung transplantation. This case highlights the advances that have been made in combining medical therapy, mechanical support systems and surgical intervention in order to functionally improve and prolong the life of patients with PAH.

Each article in this series is a reminder of the progression that has been made in the field of PH and, particularly, PAH. The establishment of screening programmes and registries, the evolution of effective diagnostic and treatment algorithms, the availability of therapies and the dedication of healthcare professionals have all contributed to vastly improving the lives and prospects of PH patients in the past decade.

STATEMENT OF INTEREST

M. Humbert has relationships with drug companies including Actelion, AstraZeneca, Bayer-Schering, Chiesi, GSK, Lilly, MSD, Novartis, Nycomed, Pfizer and United Therapeutics. In addition to being an investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. G. Simonneau has relationships with drug companies including Actelion, Bayer-Schering, GSK, Lilly, Novartis, Pfizer and United Therapeutics. In addition to being an investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. L. J. Rubin has acted on a scientific advisory committee for United Therapeutics and has acted as a consultant for NHLBI, Actelion, Pfizer, United Therapeutics, LungRx, Gilead, Aires Pharmaceuticals, GSK, Bayer, GenO and Cytokinetics. He holds shares for United Therapeutics.

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