

EDITORIAL

PULMONARY HYPERTENSION: WHERE ARE WE?

By

Majdy M. Idrees

Head, Saudi Advisory Group for Pulmonary Hypertension, Head, Pulmonary Medicine, Riyadh Military Hospital, Saudi Arabia

Email: majidrees@gmail.com

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Pulmonary Arterial Hypertension (PAH) represents a heterogeneous group of disorders shared common histological abnormalities and pathophysiology. PAH is characterized by a progressive increase of pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) leading to right ventricular afterload and failure.⁽¹⁾ The median survival from the time of diagnosis in patients with idiopathic pulmonary arterial hypertension (IPAH), formerly known as primary pulmonary hypertension (PPH), before the availability of disease-specific targeted therapy, was 2.8 years.⁽²⁾

The first reported case of pulmonary hypertension (PH) occurred in 1891 by a German physician called Ernst von Romberg, who described a patient, who at autopsy, showed thickening of the pulmonary artery but no heart or lung disease that might have caused the condition. In 1951, 39

subsequent cases were further reported and the illness received its name as Primary Pulmonary Hypertension. Unfortunately, the true incidence of PAH is still unknown. The current estimated incidence of IPAH is 1 to 2 cases per 1 million persons in the general population and the incidence of PAH in patients with other illnesses appears to vary from 2-4% of patients with portal hypertension and 0.1-0.6% of HIV patients. The incidence of PAH patients with connective tissue disease is extremely variable; prevalence ranges from 2-35% in patients with the scleroderma spectrum of disease (may reach as high as 50% of patients with limited scleroderma), 10-45% of patients with mixed connective tissue disease and in 1-14% of cases with systemic lupus erythematosus.

There may be one or more causes of IPAH; however, all remain unknown. It is believed that in most patients who develop IPAH, their blood vessels are particularly exposed to certain internal

or external injury and constrict subsequently. Diet suppressants, cocaine, HIV, and chronic hemolytic anemia are some of the factors that are thought to initiate the injury process and trigger constriction, or narrowing, in the pulmonary artery. In about 6 to 10 percent of cases, IPAH disease is considered familial and the recent identification of mutations in the bone morphogenetic protein receptor 2 (BMPR2) in the majority of cases of familial PAH has been a major advance in the explanation of the pathogenic sequence in PAH.^(3,4) Many cellular and biochemical abnormalities have been described in the pulmonary vasculature of patients with PAH that may play important roles in the development and progression of the disease.⁽⁵⁾ These include pulmonary endothelial dysfunction⁽⁶⁾ (characterized by altered synthesis of nitric oxide, thromboxane A2, prostacyclin and endothelin), impaired potassium channels, and altered expression of the serotonin transporter in the smooth muscle cells and enhanced matrix production in the adventitia.⁽⁵⁾ Characteristically, patients with PAH are found to have a higher basal level of endothelin and thromboxane A2 and lower level of nitric oxide.

In 1998 in Evian, France, a clinical-based classification of PH was proposed⁽⁷⁾ aiming to classify the disease by individualization of different categories sharing similarities in pathophysiological mechanisms, clinical presentation and therapeutic options. The subsequent 2003 Third World Symposium on PAH that was held in Venice-Italy provided the opportunity to assess the impact and the usefulness of the Evian classification and to propose some modifications Table 1. More recently, the 2008 Dana Point-USA, Fourth World Symposium put the final tuning on the classification and represents the present understanding of pathophysiology as well as of clinical-based differences or similarities within PH.

From the therapeutic standpoint, the treatment of pulmonary hypertension remains challenging and rapidly changing. This is influenced by the great

advances in our understanding of the mechanisms involved in the pathobiology of PAH, which have focused on one side upon molecular biology, developmental biology and genetics and from the other side on epidemiological and natural history studies and interventional trials. Based on these advances, the current evidence-based guidelines for the treatment of PAH were developed. The currently available disease-specific PAH therapies (that target certain pathological signals) have made significant changes in the disease natural history. Six medical therapies have received regulatory approval worldwide that target 3 different pathways: the prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway. Prostacyclin is the first and probably most potent specific therapy. It is produced predominantly by endothelial cells and it is a potent vasodilator of all vascular beds. It is the most potent endogenous inhibitor of platelet aggregation and has both cytoprotective and antiproliferative activities.⁽⁸⁾ An imbalance of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by a reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites.⁽⁹⁾ Intravenous epoprostenol for the treatment of IPAH was approved in 1995 by the FDA and considered as a landmark in the treatment stages of PAH. The prostacyclin analogue, Treprostinil, has been approved for continuous subcutaneous infusion in 2002, and for continuous intravenous infusion in 2004. In addition, the inhaled prostacyclin analogue, Iloprost, was approved in 2004. Phosphodiesterases-5 inhibitors are the second group of therapy that deal primarily with nitric oxide pathway and selectively inhibit cGMP-specific phosphodiesterases (type 5), and so augment the pulmonary vascular response to endogenous or inhaled nitric oxide.⁽¹⁰⁻¹³⁾ Sildenafil citrate, an oral phosphodiesterase type-5 inhibitor, was approved in 2005 by the FDA. The third group of disease-specific therapy is the Endothelin receptors antagonist (ERA). Endothelin-1 (ET-1) is a potent vasoconstrictor and a smooth-muscle mitogen that might contribute to the increase in vascular tone and the pulmonary vascular hypertrophy associated with PAH. Two distinct

types of endothelin-receptor have been identified, ETA and ETB. Activation of ETA receptors facilitates vasoconstriction and proliferation of vascular smooth-muscle cells,⁽¹⁴⁾ while ETB receptors activation are thought to be principally involved in the clearance of endothelin, particularly in the vascular beds of the lung and kidney leading to vasodilation and nitric oxide release. In 2001, bosentan, an endothelin ETA/ETB receptor antagonist, was the first oral therapy approved for the treatment of PAH, and in 2007, the oral ETA selective ERA ambrisentan was approved by the FDA, and the oral ETA selective ERA sitaxsentan was approved in the EU.

The big question is whether we have achieved significant benefits with the disease-specific targeted therapy?

To answer this question in an evidence-based way, we believe that we have definitely achieved positive results, as the current disease-specific targeted treatment has improved patients' exercise capacity, functional capacity, time to clinical worsening, hemodynamic parameters, overall quality of life, and survival (an increase in survival for WHO functional class III and IV patients with IPAH from a predicted survival of 33% (based on the NIH Registry) to 63% with the current therapeutic modalities). However, we have to admit that despite this 'expensive' specific treatment, PAH remains a devastating, life threatening disorder and the outcome is far from ideal. Significant number of patients (more than 50%) are suffering from residual significant exercise capacity limitation (remain WHO functional class III or IV) and continue to have very poor quality of life as reflected by frequent hospitalizations for PAH and right heart failure.

Because of this, we believe that future studies are mandatory to further improve our understanding of the pathobiology of PAH. For example, the new development in the genetic field has created a significant hope towards better disease understanding. This new technology will help us in future to pinpoint the genes that contribute to

disease susceptibility and progression, and may provide valuable help towards the identification of genetic polymorphisms that may help to predict treatment efficacy with various disease-specific targeted PAH therapeutic modalities.

So to answer the above question, we can clearly say that the outlook is promising but not ideal and the disease is only partially controlled but not cured. Many questions remain regarding the treatment of patients with PAH, e.g. what is the best way to identify patient populations who will most benefit from a specific therapy?, how to determine when treatment should be initiated?, and to establish optimal drug sequencing and combinations?. We need definitely to continue to improve our understanding of PAH if we really hope to answer all of these questions in order to give our PAH patients a hope for a 'near'-normal life.

We, in Saudi Arabia, have started our race and joined the international campaign in studying and treating the disease. We have established the Saudi Advisory Group for Pulmonary Hypertension (SAPH) in 2004 as a regional scientific body that deals with PAH patients. The mission of SAPH is to devote our effort towards the patients suffering from the disease; to educate them, support them, and to treat them. We understand the limitation of the resources, but we are doing our best. We started our national registry to study the prevalence of the disease in the Kingdom of Saudi Arabia, recently published our Saudi Guidelines on the management and treatment of Pulmonary Hypertension,⁽¹⁵⁾ and currently running an annual scientific meeting that we invite all interested physicians and patients to attend. We hope that our effort will meet the effort of the others in the Middle East countries in order to reach our target and to fulfill our mission towards our patients.

Table 1. Clinical classification of pulmonary hypertension – Venice 2003.

Class 1: Pulmonary arterial hypertension (PAH):

- Idiopathic (IPAH)
- Familial (FPAH)
- Conditions associated with:
 - Connective tissue disease
 - Congenital systemic to pulmonary shunts
 - Portal hypertension
 - HIV infection
 - Drugs and toxins
 - Other, which include thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
- Conditions associated with significant venous or capillary involvement:
 - Pulmonary veno-occlusive disease (PVOD)
 - Pulmonary capillary hemangiomatosis (PCH)
 - Persistent pulmonary hypertension of the newborn (PPHN)

Class 2: Pulmonary hypertension associated with left heart diseases:

- Left-sided atrial or ventricular heart disease, including left ventricular diastolic dysfunction
- Left-sided valvular heart disease

Class 3: Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia:

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Class 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

Class 5: Miscellaneous

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

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