Pulmonary hypertension

Advances in pulmonary hypertension

In her latest clinical update, **Priscilla Lynch** reviews the latest advances in diagnosing and treating pulmonary hypertension and speaks to Ireland's leading practitioner in the field

Pulmonary hypertension (PH) is the broad, inclusive name for a group of rare chronic diseases that affect the lungs and heart. In PH, the arteries that carry blood from the heart to the lungs narrow for reasons that are not yet entirely understood, resulting in elevated pulmonary artery pressure. Essentially, the heart struggles to pump blood through the narrowed arteries, resulting in high blood pressure in the lungs and enlargement of the heart.

This leads to increasing fatigue and progressive deterioration in exercise capacity, significantly impacting on quality of life and eventually, heart failure and premature mortality can result. The main subtypes of PH are: pulmonary arterial hypertension; heart disease/pulmonary venous hypertension; lung disease-associated PH; clots/embolic disease; and miscellaneous (see Table 2).

'Ten years ago, the only real option we had was to send patients for transplantation'

Diagnosis

PH affects more than 25 million people worldwide and there are currently approximately 200 diagnosed cases in Ireland.

It can occur from no identifiable cause, and the underlying disease process is complex. In the early stages, the patient can be asymptomatic, with an absence of clinical signs. However, as the course of PH progresses, the heart begins to fail and physical symptoms such as fatigue and breathlessness present.

The disease is often misdiagnosed, meaning correct treatment is frequently delayed, which impacts dramatically on quality of life and survival outcomes. Even with therapy, the median survival for a person living with PH is typically only five-to-six years, although timely diagnosis and better disease management can significantly improve that timeline.

The National Pulmonary Hypertension Unit at the Mater Misericordiae Hospital, Dublin, is the only one of its kind in Ireland, and it is the national referral and treatment centre for those diagnosed with PH in Ireland. The Unit provides weekly speciality consultant-led clinics and PH nurse specialist clinics and is presided over by **Prof Seán Gaine**, Consultant Respiratory Physician, who is also Chief Medical Officer with the Olympic Council of Ireland.

"Despite all the progress made with new drugs and technologies, it has consistently been the case over the past 20 years that the time from the first symptom a patient gets to the time they are diagnosed is an average of two years. So that hasn't changed, despite advanced awareness and so on, and a UK study showed that patients have to pass through an average of four different doctors before the diagnosis is made. They are often labelled as asthmatic, etc, but ultimately they continue to progress and eventually questions are asked about why they are getting worse," he told *IMT*.

Dr Gaine said if GPs and other physicians had patients presenting with unexplained breathlessness that seemed unusual, they should consider sending them for an echocardiogram in particular – which he said was the best screening tool – or an ECG or an x-ray.

"You don't want to overplay it, but it is very reasonable in the treatment of a breathless patient where the common causes don't seem to fit that on the differential diagnoses list there should be PH, because it has been demonstrated that diagnosing and treating it earlier improves the outcome," he maintained.

Treatment

Current international guidelines recommend that the management of PH take place in designated specialist centres where expert care can be provided at the correct stage of the disease process.

Therefore, Prof Gaine said doctors should feel free to refer potential and diagnosed PH patients to his clinic. "We can offer patients specialised care; we have a very dedicated team here and patients can access clinical trials for new therapies, etc."

While PH is a very serious, incurable disease, there have been significant treatment developments in the past decade. "There has been real excitement in the area over the past number of years because there have been so many new treatments launched. In the past 10 years alone we have had three new drug classes approved for the treatment of PH. In Ireland, there are six different approved drugs now. That's a lot of new drugs in any treatment area to come to the market within that time frame, so there is a lot of progress.

"Ten years ago, the only real option we had was to send patients for transplantation, whereas we don't do that quite as much now. We can keep people well longer. We don't have a cure but we certainly control the disease and we've turned a lot of it into chronic illness rather than the acute disease it used to be."

Common PH therapies, depending on the subtype and severity, include endothelin receptor antagonists, diuretics, calcium antagonists, phosphodiesterase-5 type inhibitors, and anticoagulants (Warfarin therapy has been shown to almost double three-year survival in primary PH), as well as long-term supplemental oxygen therapy.

Prof Seán Gaine: 'Specialised care'

"We're certainly seeing the benefits of the treatments we have now, which is very encouraging. The downside is we're not curing it; we're controlling it. Patients diagnosed with PH will never run again. They might walk, visit family and raise their children and so on, but there are things that we take for granted that they will never be able to do. It is a big burden to carry," Prof Gaine pointed out.

Benchmarking

As the Mater Unit is the only PH centre in Ireland, Prof Gaine is keen that it be internationally benchmarked and linked with other PH centres to ensure the best treatment and outcomes for Irish patients. There are eight specialist PH centres in the UK and together with the Mater Unit, they form the Association of Pulmonary Hypertension Centres of Great Britain and Ireland.

"I think that is very important as in Ireland, you can quickly end up being isolated and being anecdotal in your approach. It is important to be linked to bigger centres so we are achieving the international guidelines and keeping up to speed and so on, and patients are getting the best care, and [it's important] that you are benchmarked against similar peers."

Prof Gaine attends association meetings a number of times a year where he discusses patient outcomes, audits between the Mater and the UK centres, and the latest research data.

"That's really important," he explained. "For example, we have published the results of survival of PH patients across the UK and Ireland. In the UK, those centres are on a national database – in the UK you have to treat PH patients in those units only – which is the biggest database of PH patients in the world, and we are now working to add the unit here to that database, and hopefully that will happen soon."

Research and clinical trials

Internationally, there is a lot of ongoing work to develop better, more targeted therapies for PH and there have been some interesting genetic findings of late. Researchers have discovered that people with a specific BMPR2 gene mutation are more predisposed to developing pulmonary hypertension than those that do not have the gene.

The Mater Unit has developed partnerships with the Conway Institute for Bimolecular and Biomedical Science at University College Dublin. This work is looking at certain key chemical characteristics that are found in PH patients.

The Unit also participates in numerous international multicentre clinical trials for the treatment of PH. Currently, two Irish patients are involved in an international clinical trial for a new agent that is essentially a more sophisticated version of a current treatment that could play a significant role in the future management of this cohort.

Prostacyclin is used to treat PH currently but it is a very expensive and cumbersome class of drug, according to Prof Gaine. "We use it through nebulisers, every three hours, or intravenous (IV) infusions. They are serious drugs but we have an oral version we are looking at in the clinical trial currently, which is actively enrolling throughout the world and I'm hoping we will get a few more patients in there before Christmas. There is a lot of excitement about it, as it is a novel drug that seems to work.

"It is twice a day rather than a nebuliser or IV, so again if you are in a specialised centre you can have access to clinical trials like this.

"Most of the drugs that have come online for PH patients in recent years, we've been involved in clinical trials for and Irish patients have gotten them as soon as possible," Prof Gaine concluded.

Table 1: World Health Organization functional assessment classification

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and /or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Table 2: Diagnostic Classification of Pulmonary Hypertension*

Pulmonary arterial hypertension
Idiopathic
Familial
Associated with
- Collagen vascular disease
- Congenital left-to-right shunt
- Portal hypertension
- Infection with human immunodeficiency virus
- Drugs and toxins
- Other conditions

Associated with substantial venous or capillary involvement
- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis
- Persistent pulmonary hypertension of newborn

Pulmonary hypertension with left heart disease
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

Pulmonary hypertension associated with lung disease or hypoxemia or both
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Pulmonary hypertension due to chronic thrombotic or embolic disease or both
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)

Miscellaneous
Sarcoidosis, pulmonary Langerhans'-cell histiocytosis, lymphangiomatosis, and compression of pulmonary vessels (adenopathy, tumour, and fibrosing mediastinitis).

**Courtesy of www.pulmonaryhypertension.ie, the website for the National PH Unit at the Mater and its associated patient support and charity the Pulmonary Hypertension Association Ireland.*