Pulmonary hypertension

A National Pulmonary Hypertension Service for England & Wales: an orphan disease is adopted?

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A National Pulmonary Hypertension Service has been set up in the UK, recognising the need for change in the way this complex and relatively rare condition is investigated and managed in response to therapeutic breakthroughs.

In pulmonary hypertension (PH) resting mean pulmonary artery pressure exceeds 25 mm Hg at rest or 30 mm Hg during exercise. PH may complicate many different clinical disease processes or may develop as a primary phenomenon (PPH). Post mortem studies estimate the prevalence to be 1300 per million.[1] The incidence of PPH in Europe and the USA is 1–2 cases per million population per year, rising to as high as 25–50 per million per year in patients using certain appetite suppressants.[2] The mean age at diagnosis is 36 years with a female preponderance (1.7–3.5:1). There is no ethnic predisposition but familial PPH accounts for roughly 10% of cases.[3]

In patients with PPH both vasoconstriction and later thickening of the peripheral "resistance" vessel walls (remodelling) with associated thrombosis leads to raised pulmonary vascular resistance. Most of the structural changes that occur in these vessels are attributable to the proliferation of vascular smooth muscle cells. The mechanisms that initiate and propagate these changes are poorly understood. However, the recent localisation of the gene for familial PPH (PPH1) to chromosome 2q31–32 has implicated the transforming growth factor (TGF) β superfamily in the pathogenesis of the condition.[4] Environmental stimuli that may trigger the development of PPH are diverse and include ingested substances such as appetite suppressants, monocrotaline extracts, inhaled solvents, methamphetamine, cocaine, contaminated rapeseed oil, and L-tryptophan; infections, particularly HIV-1; and inflammatory disorders, thyroid disease, and circulating antinuclear and anti-Ku antibodies.[1] As a result, an imbalance in growth factors occurs in favour of promitogenic factors such as endothelin (ET)-1 and the loss of inhibitory mediators such as prostacyclin (PGI_2) and nitric oxide (NO). Endothelin-1 (ET-1) is both a potent vasoconstrictor and comitogen for vascular smooth muscle,[5] and thus has been implicated in the pathogenesis of several, if not all, forms of PH.[6]

The prognosis of untreated PPH is extremely poor with median survival times of 3–4 years. Cardiac index, right atrial pressure, and mean pulmonary artery pressure at presentation are linked to survival. Treatment has traditionally been confined to the use of antihypertensive agents, such as calcium antagonists, and anticoagulation. However, recent advances in the treatment of PH and the way in which treatment is administered are likely to change clinical practice in the UK fundamentally and may represent a paradigm for other rare or "orphan" diseases.[7] Firstly, epoprostenol, a synthetic analogue of prostacyclin (PGI_2), has recently been shown to reduce symptoms and improve survival significantly in patients with PPH, probably through its properties as a selective pulmonary vasodilator[8] and—perhaps more speculatively—through the reversal of vascular remodelling[9] and platelet adhesion. Unfortunately, epoprostenol is an onerous and expensive treatment which requires continuous intravenous infusion and can cause significant side effects. However, subcutaneous, inhaled,[10] and stable oral prostacyclin analogues been have evaluated in clinical trials and their use may obviate some of these problems. Secondly, bosentan, an ET-A and ET-B receptor antagonist has recently been found to reduce pulmonary arterial pressure acutely and to improve exercise tolerance in patients with PPH.[11] Further trials are planned in Europe within the next 12 months and other selective ET antagonists are currently under development. Thirdly, the acute pulmonary vascular response to inhaled nitric oxide (NO) seems to predict subsequent responsiveness to oral calcium channel blockade in patients with PPH, but the chronic use of NO is limited by cumbersome and expensive delivery systems. Sildenafil, an orally active selective inhibitor of monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), decreases the degradation of cGMP and promotes local release of NO thereby resulting in vasodilation. Sildenafil also has platelet antiaggregatory activity and can attenuate hypoxia induced PH and vascular remodelling in animal models. Clinical case reports suggest acceptable tolerance and symptomatic improvement following oral treatment with sildenafil alone[12] or in combination with epoprostenol in patients with PH.[13]

The potential for genetic screening and the recent emergence of these apparently effective but expensive and complex therapeutic interventions for patients with PPH is considerable and is clearly to be welcomed. However, the difficulties encountered by clinicians in gaining funding for these new treatments and in providing specialist expertise for their optimal application were recognised recently by the National Specialist Commissioning Advisory Group (NSCAG). In future, like other orphan diseases, diagnostic and treatment programmes for patients with PH will be geographically concentrated in a National Pulmonary Hypertension Service. The Service aims to deliver high quality care using nationally agreed clinical guidelines in a small number of centres (initially four in England and Wales and one in Scotland, box 1). Patient care will be provided nationwide by close collaboration with referring local physicians and the outcomes from a continuous audit process will be monitored by the NSCAG.

The development of a National Pulmonary Hypertension Service represents a

Box 1 Centres currently designated in the UK for the diagnosis and management of pulmonary hypertension

London
- Great Ormond Street Hospital for Children (children)
- Hammersmith Hospital
- Royal Brompton Hospital (adult congenital heart disease)
- Royal Free Hospital (connective tissue disease)

Cambridge
- Papworth Hospital

Sheffield
- Royal Hallamshire Hospital

Newcastle
- Freeman Hospital

Glasgow
- Western Infirmary

Where a hospital also specialises in a specific type of pulmonary hypertension this is shown in parentheses.

welcome recognition by the NHS of the need for change in the way a complex and relatively rare condition is investigated and managed in response to therapeutic breakthroughs. Other initiatives may follow.

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