Pulmonary arterial hypertension (PAH) is a rapidly progressive disorder that is lethal if it remains undiagnosed and untreated. However, modern treatments represent a tremendous advance upon the therapies available just a few years ago and the prognosis for this life-threatening disease has changed. There is now good reason to ensure earlier diagnosis of PAH among systemic sclerosis (scleroderma) patients.

PAH is defined as a mean pulmonary artery pressure (PAP) exceeding 25 mm Hg at rest or 30 mm Hg during exercise. If left untreated between 45 and 60% of patients with PAH will die within 2 yr of diagnosis [1]. However, when it occurs as a manifestation of scleroderma PAH is particularly severe and 1-yr survival following diagnosis is approximately 55% [2]. Since scleroderma patients with PAH deteriorate quickly and there is a risk of early death, speedy diagnosis, referral and treatment is vital [3]. Also, patients with PAH have a poor quality of life: they become unable to perform even routine daily tasks without severe shortness of breath, fatigue and fainting.

Pulmonary disease has emerged as a major cause of death in scleroderma patients [4]. PAH is the most likely complication of scleroderma and can develop in around 15% of these patients [5], primarily due to pulmonary vascular abnormalities or secondary to interstitial lung disease. PAH is most common in the limited cutaneous subset of scleroderma patients, and it is important that this group of patients in particular are monitored for signs of the disease. This strategy offers the potential for much earlier detection of PAH in this high-risk population than is usually possible in sporadic PAH. Patients should be encouraged to report any change in their symptoms: the earliest symptom is typically breathlessness on exertion or reduced exercise capacity. Symptomatically this may lead to dyspnoea on exertion, commonly first noted when climbing stairs or hills, although later this can occur at rest. Other symptoms that occur at later stages are chest pain due to right ventricular angina and syncopé or near syncope on exertion due to reduced cardiac reserve.

Rheumatologists have an important role in early recognition of PAH as a complication of connective tissue diseases. Anyone with dyspnoea should be carefully evaluated. Pulmonary function tests and Doppler echocardiography, supplemented by an electrocardiogram, are the traditional methods for investigating possible PAH, but their results can be misleading in scleroderma patients and definitive diagnosis requires direct measurement of PAP by right-heart catheterization.

Since around 15% of scleroderma patients may develop PAH and most cases of early PAH are likely to be asymptomatic, it is important to monitor them regularly for signs of this complication. The British Cardiac Society guidelines recommend that patients with limited cutaneous scleroderma, particularly those who are anticientromere antibody positive, should be screened by transthoracic echocardiography annually, even if they have no symptoms of PAH [6]. Screening for PAH is certainly worthwhile in these high-risk patients since it is the only way to identify PAH earlier and begin treatment early. Although PAH is incurable [6], it can now be contained for many years through use of new effective treatments for the condition. We now have a greater incentive to identify PAH patients and manage them through combined clinics, with rheumatologists working closely together with cardiologists, pulmonologists and pulmonary hypertension nurses. Since PAH is a complex disease with high morbidity and mortality, patient management should take advantage of the expertise provided by the specialist centres in the UK and Ireland.

The advantages of this multidisciplinary team approach include more effective clinical decision-making, sharing of experience and knowledge between different specialists and nursing staff and better continuity of care. This approach also makes it easier to undertake research into this disease. Shared care identifies patients suitable for state-of-the art treatment—medical and surgical—and inclusion in clinical trials. A multidisciplinary approach also allows prompt identification of patients failing medical therapy who require urgent consideration for transplantation.

Before the introduction of the prostanoids in the early 1980s the only hope for scleroderma patients with PAH was a heart–lung transplant, although this procedure was rarely performed in these patients since donor availability generally limited this option to younger patients with primary pulmonary hypertension or a small number of other isolated cardiopulmonary conditions. Patients were treated with calcium channel blockers and anticoagulants, oxygen was provided with the aim of reducing or reversing hypoxia-induced pulmonary vasodilation, and right-heart failure was treated conventionally. However, the development of long-term parenteral prostacyclin analogue infusions gave new hope for PAH patients. Iloprost, a stable prostacyclin analogue, is commonly used in the Europe and has the potential advantage of being an antifibrotic, as well as vasodilator agent. Continuous intravenous PGI2 (epoprostenol; Flolan), is commonly used and is a treatment approved by the US Food and Drug Administration (the FDA) for both primary and secondary hypertension and pulmonary hypertension caused by scleroderma spectrum disorders. The difficulties with delivering intravenous prostacyclin chronically stimulated interest in devising stable analogues of the compound that can be administered using less complex delivery systems. A stable form of prostacyclin that can be delivered via inhalation, iloprost (Ventavis®), became available in the UK in 2004 to improve exercise capacity and symptoms in patients with primary pulmonary hypertension. Two further epoprostenol analogues have also been studied—treprenol (Remodulin®), which is given subcutaneously, and beraprost, which is active orally.

The first and only licensed oral treatment for PAH, approved in the UK in 2002, is bosentan (Tracleer®). Bosentan is a treatment for PAH in patients with WHO Class III symptoms and in children down to 3 yr of age. It is the first of a new class of orally active drugs known as endothelin receptor antagonists (ERA) [7]. Endothelin (ET-1) is a key mediator of disease processes in PAH [8, 9]. Levels of ET-1 are elevated in PAH [10] and can cause vasoconstriction, inflammation, fibrosis and vascular hypertrophy [11]. ET-1 binds to two receptor subtypes, ET_A and ET_B [12]. Bosentan is a dual ERA that fully and effectively blocks the
binding of ET-1 to both ETA and ETB receptors, and prevents its harmful effects. An ETA antagonist, sitaxsentan, has also been used in an open pilot study. Results of two double-blind, randomized placebo-controlled studies show bosentan offers clinical benefits in patients with PAH [13], including significant improvements in exercise capacity and survival [12]. Long-term registry data are now being collected on PAH patients with scleroderma treated with bosentan. Since prognosis is depressingly poor in these patients, these results would appear to be a very important step forward in the treatment of scleroderma patients with PAH, as even stabilizing these patients should be considered a treatment success.

Other new treatment options include the phosphodiesterase-5 (PDE-5) inhibitor sildenafil, which is being investigated for use in PAH [14]. Trials in small numbers of patients have shown some promise and results from larger clinical trials are now expected.

There have been major improvements in PAH treatment options over the past 15 yr and drugs are being or have been developed to act on other appealing targets, including the nitric oxide pathway and 5-hydroxytryptamine. However, even though these new treatments mean we can offer our PAH patients hope, they will still have no future if we do not identify patients and treat them as early as possible, since early diagnosis and treatment are more likely to improve prognosis.

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