

Pulmonary hypertension in systemic sclerosis: a review of diagnostic and therapeutic options

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Over recent decades, advances in renal-targeted therapies in systemic sclerosis have caused a shift in the leading causes of scleroderma-related morbidity and mortality. Pulmonary arterial hypertension now confers the worst prognosis in this patient group and a large amount of time and resource is being put into developing diagnostic and therapeutic tools to improve patient outcome. Here we outline the most up-to-date evidence in this area in an attempt to improve current practice.

The term systemic sclerosis (SSc) describes a group of disorders that have in common fibrosis of the skin and viscera, microvascular change manifesting as intimal proliferation, loss of the capillary bed and a perivascular chronic inflammatory-cell infiltrate. Clinically, there are two distinct disease patterns: diffuse (D)SSc, in which there are both fibrotic and vascular changes, and limited cutaneous (lc)SSc, in which vascular rather than fibrotic changes predominate and any visceral involvement occurs late. The presence of characteristic autoantibodies suggests that SSc may arise as a result of autoimmunity. More than 90% of patients are positive for antinuclear antibodies (ANAs); anti-Scl-70 antibodies targeted against topoisomerase-1 are associated with the diffuse form and anti-centromere antibodies with more limited disease. However, it remains unclear whether activation of the immune system is a primary or secondary event in the pathogenesis of SSc.

Mortality in SSc

Over the last 25 years there has been a significant improvement in survival in SSc, as well as a change in the main causes of SSc-related deaths. Renal crisis now accounts for less than 10% of SSc causes of death, whereas before the availability of angiotensin-converting enzyme inhibitors (ACE-I) accounted for greater than 25% of deaths. Pulmonary rather than renal involvement is now the more frequent cause of death (Figure 1) [1].

Pulmonary complications in SSc

Pulmonary disease in SSc can manifest as interstitial lung disease (ILD), pulmonary vascular disease without significant fibrosis or a combination of both. Pulmonary artery hypertension (PAH) may occur as an isolated complication of SSc or secondary to cardiac disease or ILD. Isolated PAH is more common in lcSSc than in DSSc.

Pulmonary arterial hypertension in SSc

Isolated PAH in SSc is defined as a pulmonary artery pressure (PAP) of more than 25 mmHg at rest (>30 mmHg during exercise) with a normal pulmonary capillary wedge pressure (<15 mmHg) at right-heart catheterization, in the absence of significant ILD. It occurs in approximately 8% of patients with SSc [2,3] and is more common in lcSSc, but is very rarely described in DSSc.

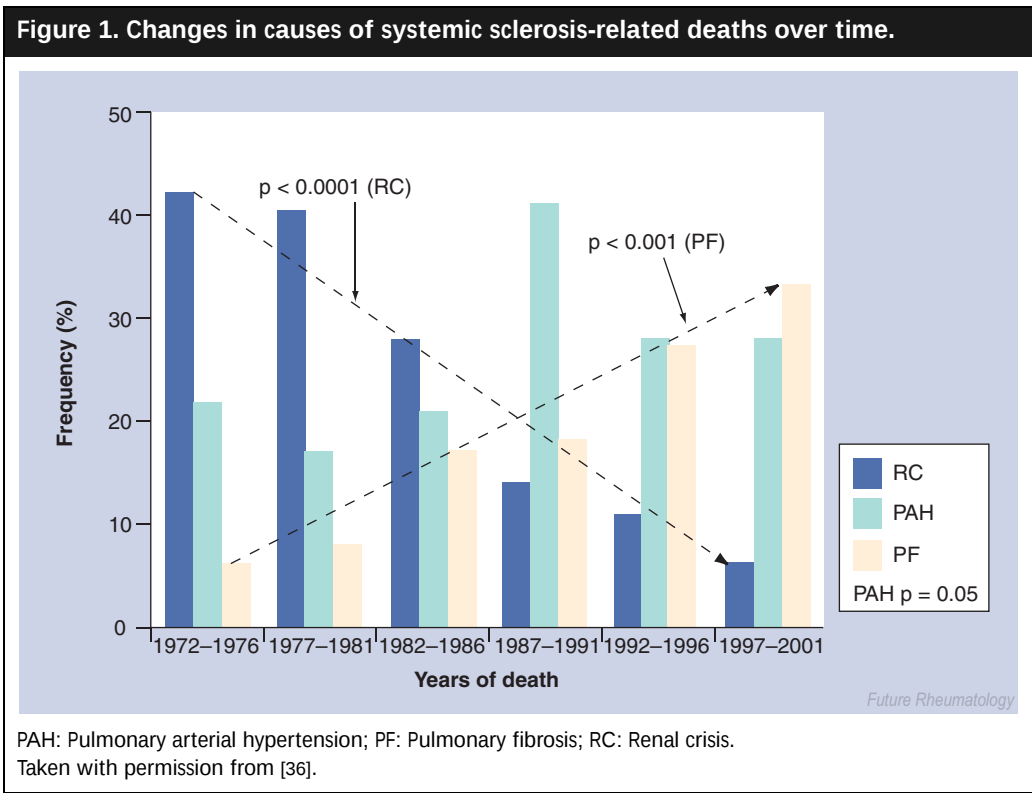
The vasculopathy that results in pulmonary hypertension in SSc is characterized by severe diffuse intimal 'onion-bulb' proliferation, medial hypertrophy with luminal occlusion of pulmonary vessels, *in situ* thrombosis and perivascular inflammatory infiltrates consisting of macrophages and lymphocytes. These changes are similar to those found in the systemic circulation. The finding of increased levels of endothelin, impaired fibrinolysis, increased platelet aggregation and mismatched vasodilating and vasoconstricting mechanisms [4] in the systemic circulation has reaffirmed the hypothesis that primary endothelial-cell dysfunction may play a central role in the pathogenesis of SSc [5].

Risk factors for pulmonary arterial hypertension in SSc

Steen and colleagues have identified several factors that are more commonly found in those who have developed PAH (Box 1) [2]. These include male gender, a later age of disease onset, Raynaud's of greater than 10 years duration, the presence of anticentromere antibodies and ANAs (anti-U3-RNP and anti-Th/To antibodies) and an isolated reduction in total carbon monoxide diffusion capacity (TLCO). Human leukocyte antigen (HLA)-B13 and HLA-B65 are found more frequently in SSc patients with isolated PAH [6].

Keywords: pulmonary arterial hypertension, scleroderma, systemic sclerosis

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Diagnosis of pulmonary arterial hypertension in SSc

Pulmonary function testing

Reduced TLCO in the presence of normal lung volumes (forced vital capacity %/TLCO% >1.8) is characteristic of patients with PAH in SSc (Box 2) [7]. A reduced TLCO has been found to be a more accurate marker of early pulmonary vasculopathy than mild elevations of PAP on Doppler echocardiography (ECHO) [8]. It is therefore recommended that all lcSSc patients should have pulmonary function testing (PFT) at the time of diagnosis, and annual measurements may be useful in those at highest risk.

Echocardiogram

ECHO can be used to estimate PAP by measuring right ventricular systolic pressure (RVSP) [9]; PAP is considered equal to RVSP in the

absence of pulmonary valve stenosis or outflow-tract obstruction. RVSP can be approximated using tricuspid regurgitant jet velocity and has been found to correlate well with invasive measurements of PAP [10,11]. Estimations of PAP can also be made using right ventricular outflow patterns [12]. Raeside and colleagues described a group of patients with connective tissue disease who, despite normal resting echocardiograms, had marked increases in PAP with exercise [13], suggesting the need for exercise ECHO, although this is not readily undertaken at present (Box 2).

Whilst ECHO is noninvasive, widely available and offers additional important information on cardiac structure and function, it has definite limitations: it overestimates the prevalence and severity of PAH, particularly in those with a PAP on ECHO of 30–45 mmHg, whilst it underestimates levels in those with high PAPs. Further work is required to identify the optimal Doppler technique to estimate RVSP and PAP and to make further comparisons with invasive measurements. Current guidelines adopted by the WHO, and UK PAH guidelines, suggest that baseline and annual PFT and ECHO should be undertaken to screen at-risk patients and identify those requiring more detailed assessment and/or treatment.

Box 1. Risk Factors for PAH in SSc.

- Limited cutaneous SSc with long duration of Raynaud's
- Male gender
- Isolated decreased TLCO with normal lung volumes
- Immunology: anticentromere and antinucleolar antibodies (anti-U3-RNP and anti-Th/To)

PAH: Pulmonary artery hypertension; SSc: Systemic sclerosis; TLCO: Total carbon monoxide diffusion capacity.

Box 2. Summary of diagnostic tools in SSC-associated PAH.

- PFT: isolated low TLCO, FVC%/TLCO% greater than 1.8.
- Transthoracic echocardiography and Doppler studies may overestimate prevalence and severity of PAH.
- WHO recommends annual PFT and transthoracic echo in asymptomatic SSc patients.
- Patients with elevated PAP measured by ECHO, particularly at-risk patients, should undergo cardiac catheterization with vasoreactivity testing.

ECHO: Echocardiography; FVC: Forced vital capacity; PAH: Pulmonary artery hypertension; PAP: Pulmonary artery pressure; PFT: Pulmonary function testing; SSc: Systemic sclerosis; TLCO: Total carbon monoxide diffusion capacity.

Cardiac catheterization

ECHO can make approximate measurements of PAPs by estimating right ventricular pressures, but more accurate readings obtained by right-heart catheterization are advised. Cardiac catheterization allows these precise measurements and also enables a detailed assessment of left and right ventricular function as well as guiding treatment by means of a vasodilator (vasoreactivity) test. Vasoreactivity testing assesses improvements in pulmonary hemodynamics (PAP, cardiac output and pulmonary vascular resistance) following direct administration of a vasodilating agent, such as prostacyclin, adenosine or nitric oxide, via a pulmonary-artery catheter. Patients whose PAP falls by at least 10 mmHg to less than 40 mmHg following administration of the vasodilating agent are deemed vasoreactive. In a previous study we have demonstrated that all patients with lcSSc and PAH have a vasoreactive pulmonary circulation to prostacyclin [14], although the debate regarding the clinical application of vasoreactivity testing continues.

Box 3. Therapeutic recommendations.

- All patients with SSc-associated PAH should receive anticoagulation unless contraindicated, in addition to diuretics and supplemental oxygen when clinically indicated (observational evidence only).
- Bosentan and sildenafil therapy are licensed for use (USA not EU) as oral therapy in patients with functional class II–IV disease.
- Currently, there is no firm evidence suggesting the superiority of endothelin-receptor antagonists or phosphodiesterase-5 inhibitors specifically in the SSc-associated PAH subgroup; both are proven to confer symptomatic benefit.
- Despite strong supporting evidence, owing to complications of administration, intravenous epoprostenol and subcutaneous treprostinil should be reserved for patients with disease unresponsive to the above measures, patients with severe class IV disease or as bridging therapy to lung transplantation.

PAH: Pulmonary artery hypertension; SSc: Systemic sclerosis.

Treatment of primary pulmonary arterial hypertension in SSc

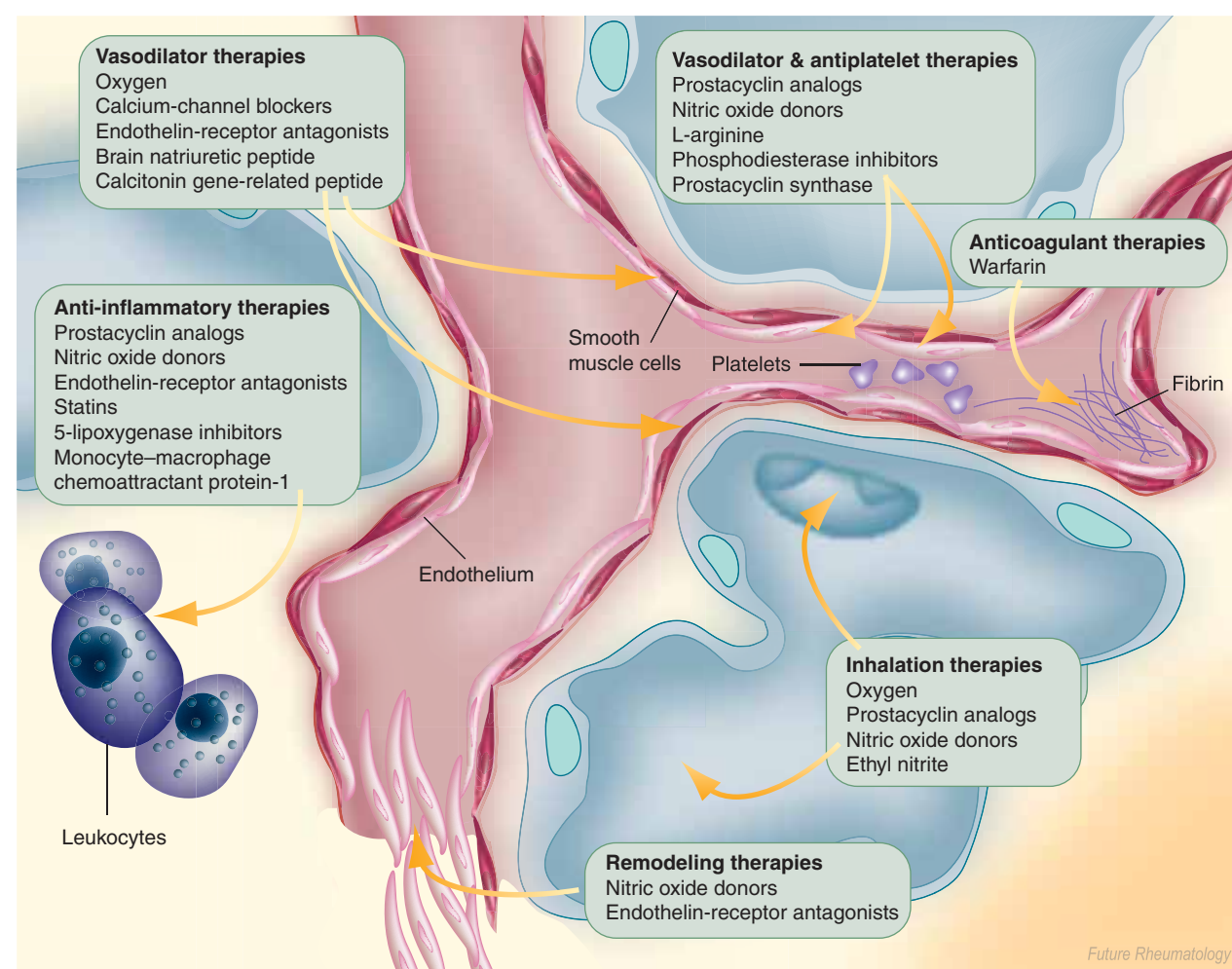
Over the last decade many treatments have become available for the treatment of PAH, both in the context and absence of SSc (Box 3). Figure 2 shows that these have been directed at many potential targets. As rheumatologists, we are in a unique position with a cohort of patients known to be at-risk of developing PAH. Unlike respiratory physicians managing patients with idiopathic disease, we have the opportunity to diagnose and treat early this devastating condition, thereby potentially altering its natural history.

Supplemental oxygen & diuretics

Hypoxemia is a potent vasoconstrictor, both directly and through its effects on endothelial cells, and is thought to contribute to the progression of PAH. It is generally considered fundamental to try and maintain systemic oxygen saturations of greater than 90% with supplemental oxygen. We found that oxygen did not improve vasoreactivity in isolated PAH secondary to lcSSc [12]. The use of diuretics may be necessary to maintain a near-normal intravascular volume in patients with right-heart failure whilst avoiding a reduction in preload, systemic hypotension, syncope and renal insufficiency.

Anticoagulation

Patients with PAH are at increased risk of *in situ* pulmonary thrombosis due to right-heart failure, dilated heart chambers, venous stasis and the disease-imposed sedentary lifestyle. There are no double-blind, randomized controlled trials (DBRCT) assessing the value of anticoagulation on symptoms, surrogate outcomes or mortality in pulmonary hypertension (PHT) secondary to any cause. A survival advantage with oral anticoagulation was observed in a subgroup of a cohort of patients with severe idiopathic PAH [15]. A further study of 64 patients with idiopathic PAH administered warfarin to patients found to have non-uniformity of pulmonary blood flow; this was found to confer a significant 5-year survival benefit in these patients [14]. There are no such studies in patients with isolated PAH due to SSc. Furthermore, its use in SSc carries the increased risk of bleeding from mucosal teleangiectasia and the potential difficulty of achieving satisfactory control because of bacterial small bowel overgrowth.

Figure 2. Therapeutic approaches to the management of pulmonary arterial hypertension.

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Calcium-channel blockers

There are no DBRCT trials of calcium-channel blockers (CCBs) in PHT. Observational studies in idiopathic PAH suggest that CCBs may confer some improvement on 1-, 3- and 5-year survival rates [16] but have to be used in very high doses (mean daily dosage: nifedipine 172 mg, diltiazem 720 mg), which confer significant undesirable gastrointestinal side effects in the scleroderma population. Their benefit in PAH is limited to patients found to be vasoreactive following vasodilator challenge during cardiac catheterization.

Angiotensin-converting enzyme inhibition

ACE-Is are thought to play a direct role in improving endothelial function in animal models and one observational study has

demonstrated an improvement in pulmonary vascular resistance in eight patients with connective tissue disease (CTD)-associated PAH (DSSc, lcSSc or mixed CTD) [17]. These results were not supported by subsequent studies. Currently, there is an ongoing DBRCT funded by the UK Arthritis Research Council, the QUINS study. QUINS assesses the efficacy and tolerability of quinapril in the management of peripheral vascular manifestations, preventing progression of visceral involvement and reducing the incidence of macrovascular complications, including PAH, in SSC.

Prostacyclin analogs

Prostacyclin is synthesized by the vascular endothelium and has both vasodilator and antithrombotic properties.

Epoprostenol

Epoprostenol is a synthetic prostacyclin analog first used in 1980 to treat idiopathic PHT. It is currently licensed for use in PHT in both the USA and UK. Its short half-life requires its administration as a continuous intravenous infusion via an indwelling catheter with a portable pump. Over the last 10 years several open-label, randomized trials have demonstrated positive effects of epoprostenol for idiopathic PAH in terms of functional capacity, walking distance and pulmonary hemodynamics [18,19]. Furthermore, the Barst study demonstrated that fewer deaths occurred during the 12-week study period in patients treated with epoprostenol compared with conventional therapies, although this was not designed as a mortality study.

The first randomized, open-label trial of epoprostenol in SSc-associated PAH specifically, demonstrated short-term improvements in exercise capacity, PAP, pulmonary vascular resistance and improved functional class when compared with conventional therapy alone (i.e., diuretics, anticoagulation, oxygen and oral vasodilators) [20], there was no assessment of survival rates in this 12-week study. No prior assessment of pulmonary vascular reactivity was undertaken; 111 patients with SSc-spectrum disease and a PAH greater than 35 mmHg without significant ILD were included. Frequent side effects, noted primarily in the epoprostenol group, included nausea, diarrhea and anorexia, whilst infusion-site problems included cellulitis, hemorrhage at the site of the catheter tip, pneumothorax and sepsis.

There are also several anecdotal reports of inhaled epoprostenol in PHT.

Iloprost

Iloprost is a chemically stable prostacyclin analog evaluated in many disorders, including the management of atheromatous-disease-related complications and Raynaud's phenomenon. It is administered intravenously, although an oral preparation has been developed. Similarly to epoprostenol, it can be aerosolized and potentially delivered directly to the alveolar membrane. Initial reports from a randomized, placebo-controlled trial of 207 patients with idiopathic PAH were promising, with results comparable to those of continuous intravenous epoprostenol trials in terms of short-term clinical and hemodynamic improvements [21]. Frequent side effects included flushing and jaw pain; syncopal episodes were more likely to be considered serious in the

iloprost group. Unfortunately, further data published on the longer-term use of inhaled iloprost monotherapy has been disappointing, with many patients requiring alternative or additional therapies and even lung transplantation in some patients [22].

Treprostinil

Treprostinil is a stable prostacyclin analog that can be administered as both an intravenous or subcutaneous infusion, it potentially has a better bioavailability than epoprostenol and a half-life of 2–4 h. Two randomized, placebo-controlled trials have studied the effects of treprostinil on idiopathic PHT and PHT associated with SSc and other connective tissue diseases in a total of 470 patients. Both analyses demonstrated improvements compared with placebo, in terms of breathlessness, hemodynamics and, to a lesser extent, 6-min walking distance when infused subcutaneously over 12 weeks [23,24]. To date, there are no long-term follow-up data on survival rates. Side effects include infusion-site pain/local reactions, diarrhea, headache and nausea. Treprostinil is currently licensed for use in the treatment of PAH in the USA but not in the UK.

Beraprost

Beraprost is another chemically stable, orally active, prostacyclin analog. To date, conflicting evidence exists regarding its efficacy in idiopathic PAH and there is little data from subgroups of patients with SSc. Beraprost does not currently hold a license in the USA or UK for the treatment of PAH.

Endothelin antagonists

There is accumulating evidence supporting the role of endothelial cells and endothelin in both idiopathic PAH and SSc-associated PAH. In both conditions it is accepted that endothelin, a potent vasoconstrictor with profibrotic properties, is produced in excess by abnormally stimulated macro- and microvascular endothelial cells [25], thus the interest in developing endothelin-receptor antagonists.

Bosentan

Bosentan, licensed for use in PAH in the EU, is an oral, nonselective endothelin-1 antagonist, which acts on both endothelin-1 receptors ET_A and ET_B. Promising results from a small, randomized controlled trial [26] paved the way for BREATHE-1 [27], which studied a total of 213 PAH patients (47 of whom had SSc-associated PAH) treated with bosentan or placebo

over 16 weeks. It demonstrated a significant improvement in 6-min walking distance (primary end point), dyspnoea index, time to clinical worsening and WHO functional class in the bosentan group as a whole. Specifically, in the SSc-patient subgroup, the authors observed a prevention of deterioration in walking distance rather than a distinct improvement in walking distance as in the idiopathic PAH group. Adverse events and toxicity, in the form of hepatotoxicity, appeared to be dose-related; the recommended dose is 125 mg twice daily. Joglekar and colleagues have retrospectively reviewed the effects of endothelin-antagonism in 23 patients with SSc-associated PAH [28]. They found bosentan to be clinically beneficial for up to 9 months in terms of WHO functional class, although there was no improvement in hemodynamics or PFTs. Clearly, further randomized, placebo-controlled trials are required to examine the longer-term effects of bosentan therapy on survival and to outline in more detail its effects on SSc-associated PAH.

Sitaxsentan

Sitaxsentan is a specific ET_A -receptor endothelin antagonist, the use of which is currently being assessed, although preliminary reports suggest it is associated with increased hepatotoxicity and has important undesirable interactions with warfarin, which are relevant in this patient group.

Sildenafil

Sildenafil is an oral phosphodiesterase type 5 inhibitor that prevents the breakdown of cyclic guanosine monophosphate (cGMP), increasing cGMP-mediated nitric oxide vasodilatation. There has been one randomized controlled trial studying the effects of sildenafil on idiopathic- and SSc-associated PAH over 12 weeks [29]. The authors studied 278 patients, 54 with SSc, and demonstrated dose-dependent improvements in PAP and WHO functional class in the sildenafil group compared with placebo. The SSc subgroup analysis demonstrated significant advantage over placebo, although less marked than in the idiopathic PAH patients, and no dose-dependent benefit was observed in terms of exercise capacity in this patient subgroup. Patients who responded to sildenafil continue in a longer-term extension study, the results of which are awaited.

Combination therapies

There are several studies that have investigated combining the aforementioned drugs in an attempt to attain further clinical and

hemodynamic improvements. These include combining sildenafil with bosentan [30], adding bosentan to epoprostenol [31] or various other prostanoids [32].

Surgical treatment

In patients with severe PAH with right-heart failure, atrial septostomy can be a useful technique. At cardiac catheterization a wire is passed across the atrial septum and balloon dilatation used to dilate the orifice until the optimum increase in cardiac output is obtained. This creation of a right–left shunt appears to be well tolerated, enhances quality of life and may improve short-term survival, often as a bridge to lung transplantation. When the above measures fail, lung transplantation is often the only remaining option in scleroderma patients with end-stage pulmonary disease [33]. Generally, these patients are considered suboptimal surgical candidates, although mortality data from one US study is comparable to that of nonscleroderma lung transplant recipients, with 1- and 3-year survival rates of 68 and 46%, respectively. In this study, one of the 24 mortalities was thought to be a result of PAH.

Summary of therapies

To summarize, few randomized controlled trials exist that examine specifically the treatment of SSc-associated PAH, the most superior published literature looks only at the short-term effects of therapies on the symptoms and hemodynamics of PAH, with no information on mortality or survival rates. In the EU, two oral preparations are licensed for use in SSc-associated PAH: bosentan and sildenafil both have evidence to support their short-term effects on exercise capacity, functional class and hemodynamic parameters (sildenafil only) in patients with idiopathic PAH and SSc-associated PAH. Whilst bosentan is the first-line recommended oral therapy in idiopathic PAH, the evidence appears to be equivalent to that for sildenafil in SSc patients. To date, there are no published long-term data looking at the effects of any therapy on mortality in this patient group. In patients with progressive, severe disease despite these measures both treprostinil and epoprostenol (licensed in the UK) confer benefit in terms of clinical, functional and hemodynamic parameters, again there is no proven effect on mortality rates.

Future perspective

Over recent years survival rates are constantly improving in SSc-associated PAH and further developments in the understanding of the disease

and the rationale behind treatment are ongoing. There is still a huge amount of work to be done on ways to improve patient selection for screening programs, to allow early diagnosis and to assess the long-term effects of the aforementioned therapies on survival rates in large numbers of patients. At the time of writing there is ongoing work on novel therapies, such as imatinib, a platelet-derived growth factor (PDGF) receptor antagonist, initially developed for use in chronic

myeloid leukemia owing to the potent mitogenic properties of PDGFs. To date, there have been three published cases reporting the use of imatinib in PAH associated with chronic myelogenous leukemia and familial idiopathic PAH, and its beneficial effects in terms of exercise capacity, functional class and hemodynamics when used in combination with failing maximal PAH therapies [34,35]. The future may see further work on the therapeutics of PDGF-receptor antagonists.

Executive summary

Definition

- Isolated pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) is defined as a pulmonary artery pressure of more than 25 mmHg at rest or more than 30 mmHg during exercise with a normal pulmonary capillary wedge pressure without significant interstitial lung disease.
- PAH is now the leading cause of mortality in SSc.

Diagnosis

- Annual pulmonary function testing and echocardiograms are recommended for all at-risk SSc patients.
- Cardiac catheterization is the gold-standard investigation in those with PAH demonstrated on echocardiogram.

Management

- Oral endothelin antagonists and phosphodiesterase-5 inhibitors are available to treat idiopathic and SSc-associated PAH. Currently the level of evidence for each class of drug is comparable.
- Parenteral or inhaled prostacyclin analogs are available for patients with advanced PAH (functional class III–IV), often as a bridge to transplant.

Future perspective

- Further randomized, controlled trials on current therapies, particularly in SSc subgroups, are required.
- Development of imatinib and other platelet-derived growth factor receptor antagonists will be undertaken.

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