Pulmonary arterial hypertension: the most devastating vascular complication of systemic sclerosis

V. McLaughlin, M. Humbert, G. Coghlan, P. Nash and V. Steen

Pulmonary arterial hypertension (PAH) is a devastating vascular complication of a number of CTDs. In patients with SSc, PAH has a dramatic impact on prognosis and survival and is the single most common cause of disease-related death. Yearly echocardiographic screening for PAH is recommended in patients with SSc. If suspected, confirmation of PAH diagnosis by right heart catheterization is necessary. Treatment goals for patients with PAH associated with SSc (PAH-SSc) aim to slow disease progression and improve quality of life. Some measures used to gauge the effect of treatment in patients with PAH-SSc remain to be fully validated; the 6-min walk distance, for example, is a simple and reproducible means of assessing exercise capacity, but there exists a need to understand what constitutes a clinically relevant change in this specific patient population. Currently, pharmacological intervention in PAH-SSc may target one or more of three pathophysiological pathways in PAH. The prostacyclin analogue epoprostenol has been shown to improve exercise capacity and haemodynamics in PAH-SSc patients and similar data are available from smaller studies on treprostinil and iloprost. The dual endothelin receptor antagonist bosentan has been shown to improve exercise capacity and haemodynamics in PAH-SSc, and similar data have been obtained in small numbers of patients treated with the endothelin receptor A antagonists sitaxsentan and ambrisentan. Impaired production of nitric oxide may be addressed by inhibiting phosphodiesterase type-5 with sildenafil or possibly tadalafil. Combinations of multiple targeted therapies may be beneficial to this patient population.

KEY WORDS: Pulmonary arterial hypertension, Systemic sclerosis, Vasculopathy.

Introduction

Pulmonary arterial hypertension (PAH), a disease of the pulmonary circulation, is defined as a mean pulmonary arterial pressure (mPAP) of >25 mmHg at rest or >30 mmHg during exercise together with a pulmonary capillary wedge pressure of <15 mmHg [1]. Sustained increases in PAP result in an increase in pulmonary vascular resistance (PVR), which in turn leads to right ventricular overload, and ultimately right ventricular failure and death [2].

Irrespective of its underlying cause, the elevations in PAP that characterize PAH are believed to occur at least in part from disturbances in the normal balance between endogenous vasoconstrictors and vasodilators in response to endothelial dysfunction or injury [3]. Simultaneously in the vasculature, there is increased production of potent vasoconstrictors such as thromboxane A2 and ET-1 and reduced production of vasodilators such as nitric oxide (NO) and prostacyclin synthase, which is required to convert arachidonic acid to prostacyclin. These abnormalities elevate vascular tone and promote remodelling of the vascular wall, which leads to the persistent increase in PVR and its adverse clinical sequelae [4].

PAH is a devastating and often fatal complication of CTDs, especially within the scleroderma (SSc) patient population, which has the highest mortality of all the rheumatic disorders [5]. In this article, we look at the impact of PAH in CTD—focusing in particular on patients with SSc—and discuss how diagnostic and treatment strategies have evolved in recent years.

Classification of pulmonary hypertension

An increased understanding of the pathophysiology of PAH has enabled important advances in the classification of pulmonary hypertension (PH). This classification has progressed from its initial separation into primary and secondary PH, via the Evian classification of 1998 [6], to today’s Venice classification (Table. 1).

The Venice classification, which arose from the 2003 Third World Symposium on PAH [2], recognizes five subclasses of chronic PH. The first of these, PAH, is commonly seen in patients with SSc. The second category is pulmonary venous hypertension, in which increased PAP arises from elevated pressures on the left side of the heart. Anything that elevates left heart filling pressures, left ventricular end-diastolic pressure or wedge pressure is transmitted back to the pulmonary vasculature and can cause PH. Potential contributors to this type of PH include systolic dysfunction, diastolic dysfunction, which is not uncommon in SSc patients, and valvular heart disease such as aortic valve disease or mitral valve disease. Because the treatment of PH associated with left heart disease is very different to that for PAH, it is important to differentiate this form of PH from PAH. The third type of PH is associated with hypoxaemia and lung disease. Anything that causes hypoxaemia can lead to modest increases in mPAP to 25–35 mmHg, whereas any type of lung disease, such as interstitial lung disease and pulmonary fibrosis, which are common in patients with SSc and sleep apnoea can also cause this type of PH. Chronic thromboembolic PH (CTEPH), which is thought to develop from single or recurrent thromboemboli at sites of venous thrombosis that fail to be reabsorbed, represents the fourth category of PH. Again, it is very important to differentiate CTEPH from PAH as CTEPH patients with proximal, surgically accessible disease may be cured with pulmonary endarterectomy. Finally, the Venice classification recognizes a fifth subclass of chronic PH that includes sarcoidosis and some unusual diseases that affect the pulmonary vasculature directly.

PAH associated with CTDs

The vascular remodelling that occurs in PAH arises from the extension of muscle into peripheral non-muscular arteries following the differentiation of pericytes and intermediate cells into
PH with lung disease/hypoxaemia

- Pulmonary arterial hypertension (PAH)

PH with left heart disease

- Atrial or ventricular
- Valvular

PH with right heart disease

- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung diseases
- Sleep-disordered breathing
- Developmental abnormalities

PH due to chronic thromboembolic and/or embolic disease

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Non-thrombotic pulmonary embolism

Miscellaneous

- Sarcoïdosis, histiocytosis X, lymphangioleiomyomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

Adapted from [2] with permission from Elsevier.

PAH is a significant and often fatal complication of CTDs, including not only SSc but also SLE, MCTD and, to a lesser extent primary SS, PM and RA [7]. Data from the French National Registry of 674 patients with PAH show that 95% of all the cases of PAH-CTD are associated with SSc (76%), SLE (15%) or MCTD [8]. Thus, PAH is a rare complication in patients with RA, SS and PM. Within the SSc patient population, prevalence of confirmed PAH is ~10–16% [7]. This is a finding borne out by other recent surveys [9]. Data from the French National Registry show that about two-thirds of the cases of PAH-SSc are patients with limited SSc and a third of cases are patients with diffuse SSc [8].

PAH is a leading cause of disease-related death in SSc patients [10], in whom outcome has historically been much worse than in patients with iPAH [11]. With median survival of just 1 year, the survival rate for patients with PAH-SSc on conventional therapy is poor (Fig. 1) [12].

Management of PAH associated with CTDs

Pulmonary complications associated with CTDs are among the deadliest and their rapid progression demands early detection and early therapeutic intervention. In the past, too many patients with PAH-SSc died prematurely because PAH was detected too late and therapeutic intervention was delayed beyond the point where it could be of any real benefit. Clearly, if PAH can be identified early in patients with SSc there is potential to intervene early to slow pulmonary vascular remodelling and improve prognosis.

Whilst routine screening for PAH in asymptomatic SSc patients is not yet available in all centres [7], results from the recent French prospective ItinérAIR-Sclérodermie study carried out in 21 SSc centres nationwide suggest that early detection is feasible [13].

In this study, 599 SSc patients without severe pulmonary function abnormalities underwent Doppler echocardiography by an experienced cardiologist at each participating centre. Patients with a peak velocity of tricuspid regurgitation (VTR) of >3 m/s or 2.5–3 m/s accompanied by unexplained dyspnoea then underwent right heart catheterization (RHC) to confirm PAH according to international guidelines (Fig. 2). Based on Doppler echocardiography, 33 of the 599 patients had suspected PAH (29 patients had known PAH). In total, 18 of the 33 patients with suspected PAH had PAH confirmed by RHC. Of these 18 patients, 14 had an mPAP of >25 mmHg at rest (five with mPAP >30 mmHg) and the remaining four exhibited an mPAP <25 mmHg at rest but >30 mmHg during exercise. The newly diagnosed cases of PAH were of mild severity [mPAP ± S.D. of 30 ± 9 mmHg; mean total pulmonary resistance (TPR) ± S.D. of 520 ± 382 dyn/s/cm5]. This contrasted with haemodynamic findings in the 29 patients with known PAH who had an mPAP of 49 ± 17 mmHg and TPR 1007 ± 615 dyn/s/cm5, indicating greater disease severity. This study is still ongoing, but should confirm if the screening algorithm can identify patients at risk of developing severe PAH. This study may also identify if early diagnosis and treatment of PAH in SSc patients can offer improved prognosis. Of note, three patients with apparently normal left-heart morphology and function on echocardiography had RHC evidence of diastolic left heart disease. In addition, 12 SSc patients with elevated VTR had normal or near-normal pulmonary haemodynamics. These observations emphasize the importance of RHC in the diagnostic approach of PAH-SSc.

While the longer-term outcome has still to be established, the ItinérAIR-Sclérodermie study has already demonstrated that screening using echocardiography can identify patients with early PAH. Echocardiography can provide estimates of PAP, and visual evidence of structural and haemodynamic changes [14]. However, in order to optimize success, proficiency in RV echocardiography is required, and diagnoses must always be confirmed using RHC [15, 16]. RHC permits direct measurement of disease haemodynamics, in which SSc patients with PAH will show evidence of an elevated mPAP (normal range 9–19 mmHg), low or normal pulmonary capillary wedge pressure (PCWP) (normal <15 mmHg), elevated right atrial pressure (normal range 1–5 mmHg), reduced cardiac index (CI; normal range 2.5–4.2 l/m2/min/m2) and increased PVR (normal range 20–130 dyn/s/cm5) [17].

Currently, the general aims in the clinical management of patients with PAH can be summarized in three statements: (i) to improve exercise capacity, New York Heart Association functional class (NYHA FC) and quality of life (QoL); (ii) to delay the time to clinical worsening; and (iii) to improve long-term outcome. Naturally, treatment goals must be tailored for individual patients, taking into account the disease stage at diagnosis, existing comorbidities, physical fitness, age and well-being.
Various measures have been used to gauge the effect of treatment in patients with iPAH and PAH-SSc, some of which have still to be fully validated in the PAH-SSc population (Table 2).

Table 2. Outcome measures in PAH for disease management and clinical trials

<table>
<thead>
<tr>
<th>Outcome measure</th>
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<tr>
<td>Exercise capacity (6MWD)</td>
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<tr>
<td>NYHA FC</td>
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<tr>
<td>Class I—no limitation of usual activity</td>
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<tr>
<td>Class II—mild limitation of physical activity</td>
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<tr>
<td>Class III—marked limitation of physical activity</td>
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<tr>
<td>Class IV—unable to perform any physical activity; dyspnoea and fatigue at rest, signs of RV failure at rest</td>
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<tr>
<td>Haemodynamic parameters</td>
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<tr>
<td>Mean PAP</td>
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<td>Right atrial pressure</td>
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<td>Cardiac output</td>
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<td>PCWP</td>
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<td>PVR</td>
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<tr>
<td>Mixed venous O2 saturation</td>
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<tr>
<td>Clinical worsening</td>
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<tr>
<td>Composite end point defined as death or deterioration severe enough to require second-line therapy, hospitalization, lung transplantation or atrial septostomy</td>
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<td>Quality of life parameters</td>
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<td>SF-36</td>
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<tr>
<td>SHAQ</td>
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<td>Biomarkers</td>
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<td>BNP and NTproBNP</td>
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<td>Survival</td>
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SHAQ: scleroderma HAQ; BNP: brain natriuretic peptide; NTproBNP: N-terminal proBNP.

Various measures have been used to gauge the effect of treatment in patients with iPAH and PAH-SSc, some of which have still to be fully validated in the PAH-SSc population (Table 2). Distance walked during a 6-min period [6-min walk distance (6MWD)] is a simple, inexpensive and reproducible test that is probably the most commonly used test in clinical trials and everyday practice. In iPAH patients, it correlates with maximal cardiopulmonary exercise testing and disease severity [18]. In the PAH-SSc population, there is still a need to understand what constitutes a clinically relevant change in 6MWD and to determine whether results should be expressed as an absolute 6MWD value or as a percentage of a theoretical value. There are also many confounding factors in the PAH-SSc population including other cardio-pulmonary disorders, restrictive heart disease, lung fibrosis, muscle pain, fatigue, arthritis, muscle weakness and contractures that may influence 6MWD.

NYHA FC, haemodynamic abnormalities and clinical worsening are considered robust outcome measures. NYHA FC enables the grading of patients from I (slight physical impairment) to IV (inability to perform physical activity at rest), offering a good means to evaluate disease progression and prognosis. In a study of patients with advanced PAH (NYHA FC III), 12 months’ treatment with the dual endothelin receptor antagonist, bosentan, resulted in about one-third of the patients improving to Class II [19]; a good outcome that correlated well with survival. Haemodynamic abnormalities, of which CI is the most important, are also robustly linked to prognosis [20]. Patients with a low CI have an extremely poor prognosis and so a key treatment objective is to normalize or improve CI. Time to clinical worsening, which is best defined as a composite end point of death, deterioration severe enough to require additional intervention such as second-line therapy, hospitalization, lung transplantation or atrial septostomy, is an outcome measure that can be used in both the clinic and clinical trials, where it provides a surrogate measure for disease progression and survival [21].

Patients with PAH want to feel less breathless and to move around more easily to improve their QoL, which is another important outcome measure in both clinical practice and clinical trials. The SF-36, a generic QoL questionnaire that covers both physical and mental parameters, and the specific SHAQ are most commonly used for assessing QoL in PAH patients and correlate with outcome [22].

In addition to the above outcome measures, there is growing interest in the potential to use biological markers to monitor response to therapy. Attention has focused on BNP, and in particular the more stable NTproBNP, the levels of which are elevated in a number of cardiac conditions including both iPAH and PAH-SSc [23, 24]. Higher BNP levels are associated with a poorer outcome in PAH patients [24] and in PAH-SSc, levels of NTproBNP have been found to correlate significantly with mPAP, RV end-diastolic pressure and PVR [25]. Although more data are needed, there are indications that post-treatment changes in BNP or NTproBNP may prove good predictors of response to therapy.
Today there are a number of outcome measures that can be used to monitor response to treatment in PAH-SSc patients. However, to optimize outcome a combination of these measures is needed in order to obtain the best possible tool to monitor disease progression and guide therapeutic management.

Progress in the treatment of PAH in SSc
Greater understanding of the pathophysiology of PAH, together with recognition that iPAH and PAH-SSc share some similarities in pathophysiology, has been accompanied in parallel by advances in treatment and improvements in survival and QoL [26].

Currently, there are three main approaches to the pharmacological management of PAH, which targets its underlying pathophysiology via the prostacyclin-, endothelin- and NO-mediated pathways (Fig. 3) [27].

The prostacyclin-mediated pathway
Patients with PAH exhibit reduced prostacyclin synthase, which is required to convert arachidonic acid to prostacyclin, a potent vasodilator and anti-proliferative agent. Treatment with synthetic prostacyclin and prostacyclin analogues aims to replenish deficiencies in prostacyclin levels in patients with PAH, including PAH-SSc, and thus promote vasodilation. Three prostacyclin analogues have been studied in PAH, mainly in iPAH patients. They include epoprostenol, a short-acting prostacyclin analogue given via continuous intravenous infusion; treprostinil, a prostacyclin analogue with a longer half-life that is administered subcutaneously, intravenously or by inhalation; and iloprost, a prostacyclin analogue that can be inhaled or administered intravenously.

A 12-week prospective, randomized, multicentre open trial compared the effects of the continuous epoprostenol infusion plus conventional therapy vs conventional therapy alone in 81 patients with severe iPAH [28]. In this cohort, intravenous epoprostenol improved exercise tolerance, haemodynamics and survival [28]. In a further randomized, open-label, controlled trial, the effects of epoprostenol plus conventional therapy vs conventional therapy alone were evaluated exclusively in patients with PAH-SSc [29]. In these patients, epoprostenol improved 6MWD by >60 m, compared with a deterioration in patients receiving conventional therapy alone [29]. As a result of epoprostenol treatment, improvements in haemodynamics but not survival were also observed [29].

Subcutaneous treprostinil has been studied in a large placebo-controlled trial of 469 patients, which included 90 patients with PAH-CTD, where it was found to improve exercise capacity (6MWD), haemodynamics and clinical events [30]. The greatest improvements in 6MWD were observed in patients who were most compromised at baseline and who could tolerate the fourth quartile of dosing. A post-hoc analysis of data from 90 patients with PAH-CTD demonstrated that continuous subcutaneous infusion of treprostinil-improved exercise capacity, symptoms of PAH and haemodynamics [31].

Additionally, inhaled iloprost has been studied in 203 patients, 17 of whom had PAH-CTD, in the AIR trial [32]. Although not a primary efficacy endpoint, the study showed that there was an improvement in 6MWD of 20 m in patients receiving inhaled iloprost vs deterioration in patients receiving placebo.

Typical side effects from prostacyclin therapy include flushing, headache, jaw pain and diarrhoea in addition to those associated with its mode of delivery such as infection and interrupted dosing in the case of intravenous epoprostenol, significant infusion site pain in the case of subcutaneous treprostinil and cough with inhaled iloprost.

The endothelin-mediated pathway
PAH is associated with excess production of ET-1, therefore blocking the effects of ET-1 via antagonism of the ETA and ETB receptors—which mediate its deleterious vasoconstrictive and mitogenic effects—is an important therapeutic strategy. Three ET-1 receptor antagonists (ERAs) have been studied in patients with PAH; bosentan, a dual receptor antagonist and sitaxsentan and ambrisentan, both of which target the ETA receptor.

In two placebo-controlled trials of bosentan in patients with PAH—Study-351 and the larger bosentan therapy for pulmonary arterial hypertension (BREATHE-1) trial—bosentan improved 6MWD by 70 and 40 m, respectively, in comparison with patients randomized to placebo [17, 21]. In both trials, time to clinical
worsening in the bosentan group was delayed compared with placebo (Fig. 4) [17, 21]. Both of these trials included patients with PAH-CTD, and in the open-label extensions of these two pivotal trials, 64 PAH-CTD patients received bosentan. Survival on bosentan was 85.9% after 1 year, and 73.4% after 2 years [33].

The recently completed TRUST study provides further support for the long-term benefits of bosentan in patients with PAH-CTD. TRUST enrolled 53 patients with PAH-CTD in NYHA FC III. After 48 weeks of treatment with bosentan, Kaplan-Meier estimates were 68% for absence of clinical worsening and 92% for survival [34].

There is also encouraging evidence from the EARLY trial that treatment with bosentan may also benefit PAH patients with early-stage disease (NYHA FC II). In this, the first placebo-controlled trial to examine the effects of specific PAH therapy in NYHA FC II mildly symptomatic PAH patient population, treatment with bosentan was associated with a significant reduction in PVR and a trend towards an improvement in exercise capacity (6MWD) as well as a delay in time to clinical worsening, a secondary end point, (77% reduction in risk; \( P = 0.0114 \)) [35]. These findings are important because they highlight the fact that disease does progress in NYHA FC II patients and that it is important to treat early-stage disease.

Sitaxsentan has been studied in two placebo-controlled trials, of which STRIDE-2 is the most important. In this study, which included 74 patients with PAH-CTD, treatment with sitaxsentan 100 mg led to a statistically significant improvement in 6MWD over the 18-week treatment period (placebo-corrected increase of 31.4 m; \( P = 0.03 \)) [36]. Ambrisentan has been evaluated in two 12-week placebo-controlled trials. ARIES-1, conducted primarily in North America, met its primary end point of 6MWD but not the secondary end point of time to clinical worsening, while ARIES-2, conducted primarily in the EU, met both the end points [37]. The integrated analysis of the two ARIES trials has demonstrated improvements in 6MWD and delayed time to clinical worsening at both the 5 and 10 mg doses.

Elevations in liver function tests are the main safety concern with ERAs and occur with all agents in this class of medicines. A recently published post-marketing surveillance study in approximately 5000 patients treated with bosentan in Europe demonstrated that liver aminotransaminases elevated \( > 3 \) times the upper limit of normal occurred at an annual rate of 10%. These hepatic effects could be managed with simple measures for combining different therapies with the aim of optimizing treatment response. This can be achieved by either the simultaneous administration of two or more targeted treatments or by the sequential administration of the absence of dose-dependent effects. In a post-hoc subgroup analysis of 84 patients with PAH-CTD in SUPER-1, sitaxsentan was observed to improve exercise capacity, haemodynamics and functional class after 12 weeks of treatment [41]. Common side effects associated with sitaxsentan include headache, flushing and heartburn and, more rarely, nose bleeds. Results of the PHIRST-1 study with tadalafil, another PDE-5 inhibitor, should be available soon.

**Combination therapy**

Although there have been major advances in the treatment of iPAH and PAH-CTD, there remains room for further improvements in symptom control, disease progression and survival. Given that currently available therapies target different pathways implicated in the pathophysiology of PAH, there is a strong rationale for combining different therapies with the aim of optimizing treatment response. This can be achieved by either the simultaneous administration of two or more targeted treatments or by the sequential addition of one or more agents to ongoing therapy. Early encouraging results have been observed in the 12-week double-blind, placebo-controlled safety and pilot efficacy trial in combination with bosentan for evaluation in pulmonary arterial hypertension (STEP) trial that investigated the addition of inhaled iloprost to ongoing bosentan (Fig. 5). Combination therapy was well tolerated in this study and led to an improvement in NYHA FC, mPAP and delayed time to clinical worsening [42].
Conclusion

PAH is a devastating complication of CTD, especially in the SSc population in which it is the major cause of disease-related death. The introduction of PAH-specific therapy designed to target pathways in the pathogenesis of disease has, however, had a major impact on patient outcomes. The potential to use novel, targeted therapies in combination may offer further improvements in survival. Results of the EARLY trial with bosantan are telling and suggest that treatment should be initiated in patients with early-stage disease. Earlier therapeutic intervention demands improved screening and diagnosis in all cases where there is high clinical suspicion of PAH.

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