Therapy of Pulmonary Arterial Hypertension in Systemic Sclerosis: An Update

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Pulmonary arterial hypertension (PAH) affects 10% to 15% of patients with systemic sclerosis and is a major cause for disease-related morbidity and mortality. Over the past decade, significant progress has been made in the understanding of the pathophysiologic mechanisms underlying PAH. This progress led to the development of several new treatment options and, as a result, dramatically improved survival among this severely affected cohort. The outcome in patients with scleroderma-related PAH is much worse than that in patients with idiopathic PAH, and unfortunately only a few studies have assessed treatment and outcome among patients suffering from connective tissue disease–related PAH. In recent years, publications of connective tissue disease subgroup analysis from large trials in PAH have emerged. We review the current treatment options for PAH and the evidence for their use in scleroderma-related PAH.

Introduction

Pulmonary complications are the most frequent cause of disease-related death in systemic sclerosis (SSc), a condition with a substantial mortality. Scleroderma can affect both the lung parenchyma and the pulmonary blood vessels. The latter occurs in some cases without significant lung fibrosis, which is termed isolated pulmonary arterial hypertension (PAH). In other cases, pulmonary hypertension occurs in association with lung fibrosis. This can represent a true secondary pulmonary hypertension due to destruction of lung tissue and chronic hypoxia, but in many cases, pathologic features of obliterative arteriopathy (ie, true precapillary PAH) are present within affected lungs. These cases should probably be regarded as mixed lung fibrosis and PAH. Recent studies using right heart catheterization to confirm the diagnosis suggest that PAH affects 10% to 15% of all scleroderma patients [1,2]. Studies using echocardiography suggest a much higher frequency, but this finding probably reflects the limitations of echocardiographic diagnosis [3•].

Over the past decade, significant progress has been made in the understanding of the pathophysiologic mechanisms underlying this condition, in tandem with the development of new treatments that significantly improved the survival in this cohort. Vasoconstriction, vascular remodeling, and thrombosis are hallmark processes in PAH [4]. Vasoconstriction has been linked to inhibition of voltage-gated potassium channels in the pulmonary arterial smooth muscle cells and to endothelial dysfunction, which leads to reduced levels of nitric oxide and prostacyclin and increased levels of endothelin-1 (ET-1). The existing treatment options for PAH address the different pathobiologic pathways underlying this condition. Currently licensed therapeutic agents in Europe include prostanoids (intravenous [IV] epoprostenol and inhaled iloprost), ET-1 receptor antagonists (ETA) (bosentan and sitaxentan) and phosphodiesterase type 5 (PDE5) inhibitors (sildenafil).

Prostanoid Therapy

Endogenous prostacyclin is a potent vasodilator and suppressor of platelet aggregation normally produced by the endothelial cells. Exogenous prostacyclin analogues emerged in the early 1990s, and two drugs are currently licensed for treatment of PAH.

Initially, in a 12-week prospective, randomized, open-label trial of 81 patients, the addition of continuous IV epoprostenol to conventional therapy (eg, anticoagulants, vasodilators) was compared to conventional therapy alone [5]. Significant improvement was seen in exercise capacity and hemodynamics (pulmonary arterial pressure [PAP] and pulmonary vascular resistance [PVR]) with significant reduction in mortality. Later, in a prospective, randomized, placebo-controlled trial of 111 patients, Badesch et al.

[6] showed similar findings. In patients with scleroderma-associated PAH (PAH-SSc), significant improvement was demonstrated in exercise capacity measured by 6-minute walking distance (6MWD) and improvement in hemodynamics, functional class, and Borg dyspnea score with a trend in favor of the IV epoprostenol–treated patients [6]. Long-term data presented by McLaughlin et al. [7] showed significantly improved survival in patients treated with epoprostenol (87.8%, 76.3%, and 62.8% at year 1, 2, and 3) compared to expected survival based on historic data (58.9%, 46.3%, and 35.4%, respectively).

Epoprostenol is delivered through a central vein as a continuous infusion necessitated by its short half-life, and interruption may lead to a rapid and possibly life-threatening symptomatic deterioration. This issue complicates treatment with the drug, and patients requiring it should be referred to specialized centers.

The short half-life of epoprostenol led to the development of more stable prostacyclin analogues including iloprost and treprostinil. The latter is suitable for both IV and subcutaneous (SC) delivery. In a series of trials IV treprostinil was compared first to IV epoprostenol and then to SC treprostinil, and SC treprostinil was compared to placebo in a double-blind fashion [8]. The results revealed that treatment with IV epoprostenol, IV treprostinil, and SC treprostinil produce similar improvement in pulmonary hemodynamics. SC treprostinil showed a trend to improve exercise capacity and pulmonary hemodynamics, although the changes compared to placebo were not statistically significant.

In a much larger double-blind, placebo-controlled trial, 470 patients were randomized to receive either continuous SC treprostinil or placebo on background of conventional therapy for 12 weeks [9]. Significant improvement was seen in 6MWD and Borg dyspnea score among the actively treated patients compared to placebo with significant improvement in pulmonary hemodynamics (PAP, right atrial pressure, and PVR). Oudiz et al. [10] analyzed the subgroup of patients participating in this study who had SSc and found significant reduction in PVR in the actively treated group compared to placebo. A trend was also seen in favor of treprostinil in terms of improvement in the other pulmonary hemodynamic parameters and 6MWD, although they did not reach statistical significance. Most recently, in a retrospective multicenter analysis, Lang et al. [11] demonstrated that the benefits from SC treprostinil treatment were maintained with significant improvement in 6MWD, Borg dyspnea score, and functional class after a mean period of 26 months. The longer half-life of treprostinil reduces the risk of serious complications due to sudden interruption of treatment.

The possibility of giving inhaled treprostinil was examined in series of randomized, open-label, single-blind studies comparing inhaled treprostinil to inhaled iloprost at comparable doses and exploring the highest possible inhalation dose and the shortest possible inhalation time [12]. Both iloprost and treprostinil led to comparable levels of PVR reduction, but treprostinil had significantly longer effect and fewer adverse reactions. The results suggest that inhaled treprostinil may be potentially useful for treatment of PAH. Currently, iloprost is the only inhaled drug licensed for the treatment of PAH. Its use was examined in a large study of 203 patients who were randomized to receive either iloprost or placebo as an inhalation for 12 weeks [13]. Iloprost significantly improved 6MWD, hemodynamic values and New York Heart Association (NYHA) functional class. The placebo-treated patients were significantly more likely not to complete the study due to death or clinical deterioration.

Beraprost, an oral prostacyclin analogue, was recently evaluated as a potential therapeutic option in PAH patients. Although the initial 12-week randomized, double-blind, placebo-controlled trial showed promising results, further evaluation in a longer 12-month study did not show a sustained benefit at 9 and 12 months [14,15]. Currently, IV epoprostenol and inhaled iloprost are the prostacyclin analogues licensed for use in PAH.

Endothelin Receptor Antagonists

ET-1 is an endogenous peptide produced by the endothelial cells. It is a potent vasoconstrictor with mitogenic, proinflammatory, and profibrotic action [16]. Its actions are mediated by two highly specific receptors: ETA and ETB. Both have been found on the surface of vascular smooth muscle cells where they mediate vasoconstriction. ETA receptors are also found on cardiac myocytes, and ETB are expressed on normal endothelial cells but are also upregulated on a wide variety of cell types in disease states. ET-1 levels have been shown to correlate strongly with PVR, mean PAP, and 6MWD in patients with idiopathic PAH (iPAH) [17]. Levels are also increased in patients with SSc, particularly associated with diffuse subset, pulmonary involvement with PAH, and renal crisis [18].

Bosentan is a dual ET-1 receptor antagonist licensed for use in patients with PAH. This licensing was based on two pivotal trials: AC-052-351 (study 351) and AC-052-352 (Bosentan: Randomised Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Arterial Hypertension [BREATHE-1]). Study 351 [19] was a double-blind, randomized, placebo-controlled trial including patients with either iPAH or PAH-SSc. Thirty-two subjects were randomized to receive 62.5 mg bosentan twice daily for 4 weeks followed by 125 mg bosentan twice daily or matching doses of placebo. A statistically significant increase was observed in the 6MWT compared to baseline among the bosentan-treated patients, and no change was seen among the subjects who received placebo. At 12 weeks, a statistically significant difference was seen between the mean 6MWD in the two groups, with an increase of 70 m among the bosentan-treated subjects and a decrease

of 6 m among the patients on placebo ($P = 0.021$). This difference was maintained at week 20. Treatment with bosentan also significantly improved cardiac hemodynamics as assessed with cardiac catheterization, improved World Health Organization (WHO) functional class, and increased time to clinical deterioration compared to placebo. Subsequently in a follow-up open-label study it was demonstrated that at 6 months, the bosentan-treated patients maintained the improvement in 6MWD [20].

In BREATHE-1, a bigger trial, Rubin et al. [21] compared two doses of bosentan (125 mg and 250 mg twice a day) with placebo in 213 patients. At 16 weeks, researchers saw a statistically significant difference in terms of 6MWT between the combined bosentan-treated groups and the group receiving placebo ($P < 0.001$), with improvement in the Borg dyspnea index, WHO functional class, and time to clinical worsening of the disease among the bosentan-treated patients.

Study 351 and the BREATHE-1 trial both included patients with iPAH and PAH associated with connective tissue disease (PAH-CTD), with the majority of the patients having iPAH. To assess the role of bosentan in the treatment of PAH-CTD the subgroups of patients with CTD who participated in the two trials and their open-label extensions were pooled and analyzed [22•]. Overall, 66 patients with PAH-CTD were randomized to participate in the two major trials (44 were treated with bosentan, and 22 received placebo). The actively treated patients showed stabilization in their exercise capacity, and deterioration in the placebo group was demonstrated by reduction in the 6MWD, although the difference between the two groups did not reach statistical significance. Bosentan also prolonged the time to clinical worsening as defined by the combined endpoint of death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement, or PAH worsening leading to discontinuation, need for epoprostenol treatment, or atrial septostomy. These results are congruent with those obtained in a recent retrospective cohort study comparing survival and hemodynamic outcome of cases of PAH-SSc treated with first-line bosentan and those treated previously. A significant advantage was seen in the bosentan treatment era compared with this historical comparator group [23••].

Antagonists selective for ETA have also been developed and evaluated as potential therapy for PAH, based in part on the possibility that blocking ETA may have greater effect on the pulmonary vasculature than blocking both receptors. For example, ETB receptors were found to mediate vasodilatation through nitric oxide synthesis [24] and were demonstrated to be essential for the pulmonary clearance of ET-1 [25]. The potential benefit from ETB receptor activation led to the development of selective ETA receptor blockers.

Sitaxentan To Relieve Impaired Exercise (STRIDE-1) was a double-blind, placebo-controlled trial of 178 patients randomized to receive placebo or sitaxentan 100 mg or 300 mg once a day for 12 weeks [26]. The primary outcome was the change in percent of predicted peak O_2 consumption during exercise, and change in 6MWT and NYHA functional class were secondary outcomes. At 12 weeks, there was statistically significant increase in the peak O_2 consumption among patients receiving 300 mg of sitaxentan but no improvement among the patients receiving placebo or 100 mg of sitaxentan. Nevertheless, significant improvement in the 6MWD was seen in both sitaxentan-treated groups compared to placebo, and no significant difference was seen between the patients receiving 100 mg and 300 mg of the drug. The mean PAP improved after 12 weeks of treatment with the 300-mg dose compared to placebo, but not in the 100-mg dose group. PVR was significantly improved in both actively treated groups, and both doses of sitaxentan improved the functional class of the patients compared to placebo.

STRIDE-1 included milder cases with PAH with no restriction for baseline 6MWD, patients with class II breathlessness and patients with PAH due to congenital heart disease. However, the STRIDE-1 study group presented analysis of a subgroup of patients in the trial who met more rigorous inclusion criteria: those with iPAH or PAH-CTD, in WHO functional classes III and IV at baseline, with a baseline 6MWD less than 450 m [27]. The analysis demonstrated even greater benefit from sitaxentan compared to placebo in terms of 6MWD, mean PAP, PVR, and WHO functional class improvement. Safety data from the STRIDE-1 trial showed that headache, peripheral edema, nausea, nasal congestion, and dizziness were the most frequent side effects. In addition, increases in the aminotransferases value greater than three times the upper limit of normal were much more common in the 300-mg dose group compared to the 100-mg dose group. Analysis of the data from the extension trial, which randomized patients to receive either 100 mg or 300 mg sitaxentan, revealed that the cumulative risk of an aminotransferase value greater than three times the upper limit of normal at 6 months was 8% for the 100-mg group and 26% for the 300-mg group, and at 9 months it remained 8% for the 100-mg group but increased to 32% for the 300-mg group. These results led to the conclusion that 100 mg is the optimal dose for sitaxentan, and the STRIDE-2 trial was set to assess efficacy of this dose compared to placebo [28].

STRIDE-2 was a randomized, double-blind, placebo-controlled trial that included 245 patients who were randomized to receive placebo or sitaxentan 50 mg or 100 mg once daily for 18 weeks. For observation only, an open-label bosentan arm was added. A statistically significant improvement in 6MWD was seen among the patients receiving 100 mg of sitaxentan and the open-label bosentan group compared to placebo, whereas improvement not reaching statistical significance was seen in the group receiving

50 mg of sitaxentan. WHO functional class also improved significantly in the 100-mg dose group with no significant change in the 50-mg group and the bosentan group compared to placebo. Time to clinical deterioration showed a trend toward improvement in the group receiving sitaxentan 100 mg and did not change compared to placebo in the group receiving 50 mg sitaxentan and the bosentan-treated group. Liver transaminase values greater than three times the upper limit of normal were observed in 6% of the placebo group, 5% in the sitaxentan 50 mg, 3% in the sitaxentan 100 mg, and 11% in the bosentan receiving group. Sitaxentan appeared to be marginally better than bosentan in terms of improvement of 6MWT and time to disease worsening and is the second ET-1 receptor blocker licensed for treatment of PAH.

Ambrisentan is another selective ETA antagonist currently being evaluated in two randomized, double-blind, placebo-controlled trials assessing safety and efficacy of three different doses of the drug. Although preliminary data is encouraging, the final results of the two trials have not yet been published.

Selective Phosphodiesterase Type 5 Inhibitors

Cyclic guanosine monophosphate (cGMP) mediates the pulmonary vasodilating effect of nitric oxide and is degraded in the lung mostly by PDE5. Sildenafil selectively inhibits PDE5 and thus increases the levels of cGMP and enhances nitric oxide–mediated vasodilatation. The efficacy of sildenafil for treatment of PAH was tested in a 12-week double-blind, placebo-controlled trial, the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study [29]. In this trial, 278 patients were randomized to receive placebo or sildenafil in dose of 20 mg, 40 mg, or 80 mg three times a day. There was statistically significant improvement in 6MWD, PAP, PVR, and WHO functional class at 12 weeks in all sildenafil-treated groups compared to placebo, but no significant change in Borg dyspnea score and time to clinical worsening. Badesch et al. [30] did a subgroup analysis of the 84 patients with CTD participating in the SUPER study. The results showed that sildenafil improves exercise capacity, WHO functional class, and cardiac hemodynamics compared to placebo, but clear benefit was observed only with the lowest dose of 20 mg three times a day. The SUPER study showed that sildenafil is relatively safe and effective agent for treatment of PAH.

In the Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study, 26 patients were randomized to receive either bosentan 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for 12 weeks or sildenafil 50 mg twice daily for 4 weeks followed by sildenafil 50 mg three times a day [31]. No significant difference was seen between the two groups in terms of right ventricular mass change, exercise capacity and change in N-terminal pro-brain natriuretic peptide levels. Sildenafil is now licensed for the treatment of PAH. Two other PDE5 inhibitors (tadalafil and vardenafil) have been candidates for treatment of PAH, and the Tadalafil in the Treatment of Pulmonary Arterial Hypertension (PHIRST-1) trial is currently recruiting patients.

Combination Therapy

In recent years, the use of more than one agent targeting different pathophysiologic mechanisms in PAH has emerged as a logical step. The rationale for combining different complementary approaches was provided by studies assessing the efficacy of various combinations of existing treatments. The BREATHE-2 trial assessed the efficacy of added bosentan to epoprostenol against epoprostenol alone in 33 patients with PAH [32]. Although the increases in exercise capacity and hemodynamic parameters were not statistically significant, the results showed trend in favor of the combined regimen.

In a randomized, double-blind, placebo-controlled trial McLaughlin et al. [33] demonstrated that the addition of inhaled iloprost to a stable dose of bosentan significantly improves time to disease worsening and pulmonary hemodynamics. In the actively-treated group compared to placebo, an improvement was seen in 6MWD, which almost reached statistical significance ($P = 0.051$). Several acute studies confirmed that sildenafil and inhaled iloprost act synergistically, and the combination caused significantly greater reduction in PAP compared to iloprost alone [34,35]. Hoeper et al. [36] demonstrated that in patients who did not have a sustained response to bosentan alone after median follow-up of 11 months addition of sildenafil significantly improved 6MWD, and the effect was maintained for a median follow-up of 9 months with no treatment-related serious adverse events or deaths.

In a recent study, researchers compared outcomes in patients treated with prostanoids as a monotherapy (historical control group) and patients treated after 2002 [37]. The availability of bosentan and sildenafil prompted a new approach in treatment of patients with PAH in NYHA class III and IV. Treatment goals included 6MWD greater than 380 m, peak O_2 uptake greater than 120 mm Hg and peak systolic blood pressure during exercise greater than 120 mm Hg. Bosentan was used as a first-line treatment, and when treatment goals were not met, it was combined with sildenafil. The addition of inhaled iloprost was considered if sildenafil and bosentan were not effective. If the set treatment goals were not achieved IV iloprost and ultimately lung transplantation were considered. This approach led to significantly higher overall survival ($P = 0.047$), transplantation-free survival ($P = 0.007$), and survival without transplantation or IV prostanoid ($P = 0.002$) among the treated patients compared to a historical cohort. The current American College of Chest Physi-

cians and European Society of Cardiology guidelines for treatment of PAH suggest bosentan as a first-line treatment agent in patients in functional class III. Combination therapy is recommended in patients failing to respond to monotherapy [38,39••].

Immunosuppression in SSc-PAH

The role of immunosuppressive agents in the treatment of PAH remains unclear. Recently published results of a single-center, retrospective study of 28 patients with CTD showed that unlike patients with PAH associated with systemic lupus erythematosus (SLE) or mixed connective tissue disease who may benefit from IV cyclophosphamide treatment, immunosuppression does not improve PAH-SSc [40]. Currently, immunosuppressive therapy is generally considered appropriate in PAH only if there is clear evidence of an active vasculitis or SLE, and it should probably be given in addition to other more specific PAH therapies as discussed above.

Screening for PAH in SSc

Patients with PAH-SSc have substantially higher mortality than patients with iPAH [41]. PAH is a relatively common complication of SSc, and although the prognosis is still poor, considerable advancements in treatment have led to significantly improved survival [23••,37]. All patients diagnosed with SSc should be kept under regular follow-up for monitoring of any clinical symptoms and signs suggestive of disease-related complications including PAH. No clear guidelines exist describing the need for screening for PAH in SSc patients, although some authors suggest that annual echocardiography should be performed in all SSc patients [42]. The current noninvasive screening tests do not have the sensitivity and specificity to reliably confirm or exclude diagnosis of early PAH; therefore, they should be interpreted within the clinical context [43,44]. The European Society of Cardiology is unclear on the topic of screening in their guidelines on diagnosis and treatment of PAH [39••], but the American College of Chest Physicians guidelines for screening of PAH recommend that patients at risk of PAH (including patients with SSc), even if asymptomatic, should undergo transthoracic Doppler echocardiography [38]. At the Centre for Rheumatology and Connective Tissue Diseases at the Royal Free Hospital, we aim to perform annual echocardiography, electrocardiogram, and pulmonary function testing in all patients with diagnosis of SSc as part of their continuous regular follow-up. Suspicion of PAH based on clinical picture and screening test results should prompt referral to a specialist center where the diagnosis can be confirmed by right heart catheterization.

N-terminal Pro-brain Natriuretic Peptide: A Potential Surrogate Marker in PAH-SSc

The plasma levels of N-terminal pro-brain natriuretic peptide (N-T proBNP) recently emerged as a relatively powerful noninvasive tool for diagnosis of PAH. Initially in a pilot study of 49 SSc patients (13 with and 26 without PAH), Mukerjee et al. [45] demonstrated statistically significant correlation between plasma levels of N-T proBNP and mean PAP, right ventricular end diastolic pressure, and PVR with a cut-off value 395 pg/mL, having sensitivity of 69% and specificity of 100% in this patient population. Later in a larger prospective study of 109 patients with SSc, Williams et al. [46] confirmed strong correlation between levels of N-T proBNP and cardiopulmonary hemodynamics, exercise capacity, and WHO functional class. There was also strong correlation between N-T proBNP and mortality, with a fivefold increase in the risk of death for every 10-fold increase in baseline N-T proBNP and fourfold increase in the risk of death for every 10-fold increase in follow-up N-T proBNP level. At a cut-off point of 395 pg/mL, the test had sensitivity of 56% and specificity 95% with positive predictive value of 95% and negative predictive value of 56.5%. These results show that N-T proBNP levels have similar positive and negative predictive value to echocardiography, although further evaluation in larger cohorts is needed.

Conclusions

Although there have been major advances in terms of new treatments for PAH leading to improved survival, there have been relatively few trials prospectively evaluating treatments for PAH-SSc in particular. Most treatment approaches are drawn from experience in iPAH. Because the outcome of iPAH is consistently superior to PAH-SSc, this may not be the best approach. Comorbidity due to other disease manifestations may confound assessment and treatment in PAH-SSc, and cases may be treated earlier than in iPAH due to the introduction of prospective screening programs. The best way to harness the advances in PAH therapy and apply them to SSc remains to be established by prospective clinical trials. Poor outcome and the considerable expense that these treatments entail should be important drivers of progress. We are reminded of the unique therapeutic challenge that SSc poses to practicing rheumatologists.

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