Update in systemic sclerosis-associated pulmonary arterial hypertension

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Summary

Pulmonary arterial hypertension (PAH) is one of the leading causes of death in systemic sclerosis (SSc). Despite advances in treatment options for PAH, long-term prognosis remains poor for scleroderma-associated PAH (SSc-PAH). Although prompt diagnosis and treatment of PAH may have significant impact on survival rates, early detection of the syndrome continues to be challenging in SSc due to several factors ranging from limitations of the current screening tools and the complexities of the disease. In comparison with other PAH subgroups, SSc-PAH patients respond poorly to conventional forms of PAH therapy. Recent findings indicate that factors such as autoimmune and inflammatory responses, more severe vasculature remodeling, and intrinsic cardiac involvement may account for these differences.

Pulmonary arterial hypertension (PAH), defined by an elevated mean pulmonary arterial pressure (mPAP) greater than 25 mmHg and a pulmonary capillary wedge pressure less than 15 mmHg, is a progressive disorder involving the pulmonary vasculature that leads to right heart failure and death [1]. PAH is a well-recognized complication of systemic sclerosis (SSc) with a prevalence between 10 xw and 12% [2–5]. SSc-associated PAH (SSc-PAH) is a leading cause of PAH in all PAH registries in the western world [6–8]. SSc-PAH has a dramatic impact on clinical course and overall survival, and remains a leading cause of mortality in SSc [9]. Despite recent advances in PAH leading to the development of disease-targeted therapies for idiopathic PAH (IPAH), patients with SSc-PAH are frequently less responsive to therapy with overall worse outcome compared to IPAH [10–13]. While it remains unclear why SSc-PAH behaves differently...
from other PAH categories, several factors may come into play such as limitations of the current disease markers and clinical tools that have been used to evaluate treatment response. This article focuses on the clinical features of SSc-PAH and emerging strategies for the assessment and management of the disease.

**Epidemiology**

**Prevalence and incidence**

Establishing the diagnosis of SSc-PAH requires hemodynamic data obtained by right heart catheterization (RHC) and exclusion of other entities such as left ventricular dysfunction, and significant lung parenchymal disease [1]. SSc-PAH represents around 15–30% of PAH in most registries, however, estimating the incidence and prevalence of PAH in SSc has been as challenging as for PAH in general [9,10]. This may be related to multiple factors, including inclusion and exclusion criteria that may vary according to registries or screening and diagnostic protocols [12]. For instance, a prevalence of 5 to 60%, was previously estimated when less strict diagnostic criteria were adopted [3,11,14–16]. It is now, however, accepted that the prevalence of PAH is about 10% in SSc when the diagnosis relies on strict hemodynamic criteria. Knowing that the overall prevalence of SSc is between 80 and 200/million, it follows that the prevalence of SSc-PAH may be as high as 20/million and thus higher than the prevalence of IPAH estimated at 2–6/million [4], although this is not reflected in most large registries [4,17] suggesting that the diagnosis of SSc-PAH may be vastly under-recognized.

**Risk factors**

Patients with SSc represent a population at risk for developing PAH, thus it becomes paramount to recognize susceptible patients in order to facilitate early monitoring and detection. Certain clinical characteristics, including limited SSc, late age onset, longstanding disease (> 10 years) and a reduction in the diffusing capacity of carbon monoxide (DLCO), have been associated with the development of PAH [18–22]. For example, patients with limited cutaneous SSc, with positive anti-centromere antibody and increased numbers of cutaneous telangiectasia, are more likely to develop PAH [23,24]. While patients with diffuse cutaneous SSc are at less risk of developing PAH, they may, however, develop pulmonary hypertension at any stage in their disease in the setting of progressive interstitial lung disease (Group 3 disease of the World classification) [25]. It also appears that patients who develop SSC later in life are at higher risk of developing PAH [26].

A progressive isolated reduction of DLCO is associated with the development of PAH in patients with SSc [27]. A recent report from the PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) registry, an ongoing prospective registry involving 22 SSC centers in the US, revealed that the characteristics of the approximately 131 SSC patients who developed PAH included age > 60 years old, female gender (84%), limited cutaneous SSc (90%), and a DLCO < 50% predicted [28].

**Pathogenesis**

Inflammation is increasingly recognized as a pathological hallmark in PAH as suggested by infiltration of inflammatory cells in pulmonary perivascular spaces within and around plexiform lesions [29–31]. In addition, increased levels of inflammatory markers such as macrophage inflammatory protein-1α, IL-1β and IL-6, and P-selectin are observed in severe forms of IPAH [32–36]. Whether this inflammatory process leads to a state of imbalance between vasoactive, growth factors and proliferative mediators leading to aberrant regulation of endothelial and smooth muscle cells as well as fibroblasts, and vascular dysfunction remains unclear [37]. SSc-PAH shares similar histological features with IPAH, including intimal hyperplasia, medial hypertrophy, adventitial fibrosis, and inflammatory infiltrates. However, there are fewer plexiform lesions, increased intimal fibrosis, more heterogeneity, and a higher prevalence of veno-occlusive lesions when compared with IPAH [38–41].

**Autoimmunity**

Autoimmunity appears to be a central component of pulmonary vascular remodeling in PAH. Characteristic vascular changes, in the form of endothelial cell apoptosis, increased expression of cell adhesion molecules due to endothelial cell activation, inflammatory cell recruitment, a procoagulant state, intimal proliferation and adventitial fibrosis leading to vessel obliteration, has been described in early stages of SSc [42–46]. Increased levels of soluble circulation forms of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin have been reported in SSc, and likely reflect endothelial injury [47–49]. Similarly, increased levels of circulating vascular endothelial growth factor (VEGF) and angiostatic factors in SSc have been observed [50–53]. Enhanced VEGF levels, a glycoprotein that induces proliferation, migration and increased vascular permeability, may reflect impaired angiogenesis or altered signalling in SSc. Dysregulated angiogenesis appears to be a key pathological feature in SSc-PAH and could be the focus of future studies as a potential therapeutic target.

Autoantibodies are present in SSc, both classical including anti-topoisomerase I, anti-centromere proteins, anti-RNA polymerase I/II, anti-polymyositis/scleroderma, anti-fibrinogen (U3RNP), anti-Th/To, as well as non-nuclear autoantibodies such as anti-matrix metalloproteinases 1–3 (Anti-MMP 1 & 3), anti-platelet-derived growth factor (anti-PDGFl), anti-steroidal anti-inflammatory drug-activated gene (anti-Nag-2), anti-fibrin-1 (anti-FBN 1), and anti-endothelial cell antibodies (aECA) [54]. In SSc-PAH, these autoantibodies are often linked to the development of certain phenotypes in SSc.
with subsequent development of PAH. For instance, anti-U3RNP is more prevalent in patients with SSc-PAH [55]. Although autoantibodies correlate with SSc severity, their direct pathogenic relevance has yet to be established. Progress in this area has been hindered by current techniques for identification of autoantibodies that utilize transformed epithelial cell lines (where there is detection of only shared groups of autoantigens) that fail to detect phenotype-specific autoantigens uniquely expressed in target cells, such as the endothelial cell [56]. Despite this and other limitations, there is growing evidence supporting a pathogenic role of specific autoantibodies in SSc and potentially in SSc-PAH. Antibodies to fibrin-bound tissue plasminogen activator in patients with limited SSc and anti-topoisomerase II-a antibodies, particularly in association with HLA-B35 antigen, have been reported in SSc-PAH [57]. IgG antibodies directed against endothelial cells and obtained from patients with IPAH and SSc-PAH display distinct reactivity profiles against antigens from micro- and macro-vascular beds [58,59]. aECA, which can activate endothelial cells, enhance the expression of adhesion molecules and trigger apoptosis, and are associated with digital ischemia and PAH [30,60]. Antifibroblast antibodies, found in the serum of patients with SSc-PAH, are suspected of causing fibroblast dysfunction leading to pulmonary vascular wall remodeling [61]. The detection of antifibroblast antibodies in the serum of SSc patients has significant pathogenic importance because these antibodies can activate fibroblasts and induce collagen synthesis, thus potentially contributing directly to the remodeling process. In fact, antibodies from sera of patients with SSc can induce a pro-adhesive and proinflammatory response in normal fibroblasts [62]. Antifibroblast antigens recognized by serum IgG from IPAH and SSc-PAH patients that have been identified include proteins involved in regulation of cytoskeletal function, cell contraction, oxidative stress, cell energy metabolism, and other key cellular pathways [63]. Furthermore, angiotensin II type 1 receptor and endothelin-1 type A receptor antibodies have been recently described in patients with SSc [64]. It is quite intriguing that higher levels of angiotensin II type 1 and endothelin-1 type A receptor antibodies are associated with more severe disease manifestations and predict SSc-related mortality. Of particular interest is that both autoantibodies induced extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and increased transforming growth factor β (TGF-β) gene expression in endothelial cells, signaling pathways that could be blocked with specific receptor antagonists.

Genetics
While several gene alterations have been uncovered in heritable PAH within the last decade, including identification of numerous alterations in the bone morphogenetic protein receptor type 2 (BMPR2), mutations in activin A receptor type II-like kinase-1 (ACVR1 which encodes for the TGF-β receptor) in patients with PAH and hereditary hemorrhagic telangiectasia (HHT), to date, no studies have identified the presence of BMPR2 mutations in SSc-PAH [65,66]. Furthermore, Caveolin-1 (CAV1), which encodes a membrane protein of caveolae abundant in the endothelium and other cells of the lung, is a novel gene for heritable PAH (HPAH) that was identified in the absence of any TGF-β [67]. Austin et al. demonstrated a reduction in caveolin-1 expression by immunostaining within the endothelial cell layer of small arteries. More recently, Ma et al. identified a heterozygous novel missense variant in the potassium channel KCNK3 [68] which encodes a pH-sensitive potassium channel in the 2-pore domain superfamily [69], is sensitive to hypoxia, and plays a role in the regulation of resting membrane potential and pulmonary vascular tone [70–72]. Alterations in these genes have not been specifically explored in SSc-PAH. On the other hand, Wipff et al. showed significant difference in the frequency 6-base insertion in intron 7 of endoglin between SSc patients with and without PAH and between SSc-PAH patients and controls [73]. Other genetic studies have identified associations with polymorphisms in inflammatory genes, such as IL-1β, IL-2, and TNF-α-induced protein 3, and SSc subtypes [74,75].

Clinical features
Patients with SSc-PAH tend to be asymptomatic early in the disease or only have symptoms related to involvement of other organs by SSc. Clinical symptoms are non-specific, including progressive dyspnea with exertion which is the most common initial presentation, however, functional impairment may be confounded by overall dysfunction from SSc disease and concomitant musculoskeletal disease. Physical examination findings may be absent early in the disease, however, signs of right ventricular (RV) dysfunction become more evident as the disease progresses. Clinical findings include prominent jugular venous distention and/or right atrial enlargement. In addition to vascular involvement, other organ systems are commonly affected in SSc. Renal disease is prevalent, and may be more common than in IPAH [76]. Direct cardiac involvement can also occur, affecting the myocardium, pericardium and/or small intramyocardial vessels by vascular, fibrotic and inflammatory changes [77]. These processes may lead to left ventricular (LV) dysfunction; there is a higher prevalence of non-systolic LV dysfunction as assessed by echocardiography in SSc-PAH compared with IPAH [78]. Furthermore, SSc-PAH patients more commonly present with pericardial effusion compared to IPAH, although it remains unknown whether the effusions are related to progressive RV dysfunction or to the underlying inflammatory processes [79,80].

Hormonal and metabolic dysfunction is also common; N-terminal pro-brain natriuretic peptide (NT-proBNP), a neuro peptide
released in response to ventricular stretch, is frequently elevated in SSc-PAH and appears to be significantly higher than in IPAH patients with similar hemodynamic perturbations [81]. Similarly, metabolic alterations such as hyponatremia are common in SSc-PAH and portend a poor prognosis [82].

Cardiac involvement and hemodynamics

As previously discussed, myocardium involvement is a well-recognized clinical feature of SSc causing fibrosis and impaired microcirculatory function in up to 50% of patients [77,83]. When compared with other forms of PAH, patients with SSc-PAH are more likely to have left heart abnormalities [84,85]. These include LV hypertrophy, non-systolic LV dysfunction, and left atrial enlargement [86]. In addition, SSc-PAH patients are more prone to conduction abnormalities [87]. As for hemodynamic parameters, SSc-PAH patients typically have less severe hemodynamic impairment compared to IPAH [78]. However, traditional hemodynamic measures of disease severity, such as cardiac index (CI) and right atrial pressure (RAP), which have previously been demonstrated to strongly predict survival in IPAH, are inconsistently associated with outcomes in SSc-PAH [76,78,88]. However, a recent meta-analysis by Lefevre et al. suggested that in fact the majority of prognostic hemodynamic factors in IPAH, such as mPAP and right atrial pressure (RAP) (as well as functional assessment with the 6-minute walk distance), were just as reliable as prognostic factors in SSc-PAH [89].

RV adaptation to the increased cardiac load is the main determinant of outcome in PAH [90]. RV dysfunction in SSc is yet to be fully elucidated, however, pulmonary afterload and primary cardiac depression are broadly considered as major contributors for worsening RV function [91]. A report by Overbeek et al. showed, based on indirect measurements, that RV contractility is lower in patients with SSc-PAH than in IPAH [92]. Consistent with this observation, a recent study from our group demonstrated that intrinsic RV myocardial function is significantly depressed in SSc-PAH compared with IPAH at similar pulmonary vascular afterload [93]. These findings support the notion that intrinsic RV systolic dysfunction in SSc, which leads to inability of the RV to compensate for higher afterload, rather than differences in afterload may be responsible for SSc-PAH poor survival.

Musculoskeletal involvement

Musculoskeletal involvement is a frequent complication in patients with SSc and a major cause of disability. Joint involvement has been described in over 60% of SSc patients, while muscle involvement was found in around 80% of patients [94]. Despite its functional impact, which can interfere with the patient’s ability to perform a routine 6 minute walk test, musculoskeletal involvement is unlikely to significantly affect overall survival [94].

Evaluation

Screening for SSc-PAH

Unfortunately, early identification of patients with SSc-PAH remains challenging due to the natural history of the disease and limited screening tools. Several organizations, including the American College of Cardiology, American College of Chest Physicians, American Thoracic Society, Pulmonary Hypertension Association and the European Society of Cardiology/European Respiratory Society have published a variety of screening recommendations relying mainly on abnormal findings on transthoracic echocardiography (TTE) [1,95]. The implementation of these recommendations still varies between different institutions and clinicians [96–98]. Further, other clinical tools such as DLco, alone or in combination with NT-proBNP, may not be routinely obtained by clinicians [27,99]. Recently, the DETECT study group, the first screening study to undertake systematic RHC in a cohort of SSc patients for diagnosis of PAH, suggested an algorithm using simple clinical data and non-invasive tests for early identification of PAH in a mildly symptomatic population [100]. The rate of RHC required in the high-risk SSc population included in DETECT was 62% compared to 40% when the ESC/ERS guidelines were applied. However, the proportion of RHC performed that did not confirm a diagnosis of PAH was similar between the DETECT algorithm and the ESC/ERS guidelines (65% vs 60%). Further, detailed recommendations have been recently published by Khanna et al. for early screening and detection of PAH in SSc [101]. It was recommended that screening pulmonary function tests (PFTs) with single breath DLco, TTE, and measurement of NT-proBNP be performed in all patients with SSc as soon as any new signs or symptoms suggestive of PH develop. Further, the authors recommended PFTs and TTE be performed annually in all SSc patients. Several other techniques have been proposed for SSc-PAH screening. The tricuspid regurgitant jet velocity (TVR) obtained by TTE, the most commonly used screening tool, provides an estimate of the pulmonary arterial systolic pressure (PASP). Although a number of studies have demonstrated reasonable correlations between PASP estimated TTE versus RHC, there are some limitations to this echocardiographic technique including occasional poor visualization of the regurgitation envelope and operator related technical problems [102–104]. Other echocardiographic measures, such as the tricuspid annular plane systolic excursion (TAPSE), may offer an easily obtained, reproducible measure of PAH severity and RV function that may be useful in both IPAH and SSc-PAH [105].

Cardiac MRI is being utilized with increasing frequency in the assessment of PAH in general and SSc-PAH in particular. Besides parameters of RV size and function, we and others are examining by these and other methods the interaction between the pulmonary vasculature and the RV in SSc-PAH in hopes of elucidating specific novel markers of disease.
Outcome measures in SSc-PAH

In addition to the challenges in screening and diagnosing PAH in SSc patients, it is apparent that outcome measures currently utilized in the assessment of PAH may not be adequate or appropriate in SSc-PAH. For instance, as noted previously, RAP and CI were thought not to be predictive of survival in SSc-PAH despite being strongly associated with outcome in IPAH. Regarding the 6MWT, it should be noted that this outcome measure has not been adequately validated in SSc-PAH [106,107]. Furthermore, the minimally important difference (MID) for the 6MWT, defined as the smallest difference in an outcome measure that identifies a clinically meaningful change in outcome as opposed to a relying solely on statistically significant change in outcome, has yet to be defined in SSc-PAH. While the MID has been recently described in a large cohort of patients with PAH from the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study, the small number of SSc-PAH patients included in the study prevents the determination of the MID for this subset [108,109]. Further limitations to the utility of the 6MWT in SSc-PAH include the impact of musculoskeletal disease and subclinical ILD upon the distance achieve [107,110]. These factors affecting the total distance achieved have important implications regarding prognosis and assessment of response to therapy since prior studies in IPAH patients have identified clinically important 6MWT distance thresholds both at baseline and after th [106,111,112]. Other non-invasive measures have been studied as potential outcome measures for PAH and SSc-PAH in particular [113]. Serum markers, such as uric acid, may be somewhat useful for prognosis in IPAH, but neither the relevance in SSc-PAH or the responsiveness to PAH-specific therapy have been described [114]. Serum NT-proBNP has been demonstrated to correlate with disease severity and predict survival in IPAH [115]. Several reports suggested the utility of NT-proBNP to predict the development of PAH in SSc and to predict survival in SSc-PAH [99,116]. Furthermore, our experience suggests that NT-proBNP levels significantly differ between IPAH and SSc-PAH despite similar hemodynamic characteristics and that NT-proBNP predicts survival only in SSc-PAH, emphasizing the potential role of NT-proBNP in the assessment of PAH in SSc patients [81].

Treatment

With improved understanding of the pathogenesis of PAH, novel therapies targeting select pathways have been developed, with a focus on the chronically impaired endothelial function, affecting vascular tone and remodeling [117–119]. More recently, the observation of aberrant proliferation of endothelial and smooth muscle cells in PAH, with increased expression of secreted growth factors, has led some investigators to consider PAH a quasi-neoplastic process [120,121]. While this reasoning may be somewhat hyperbolic, antineoplastic agents have already been tried recently in PAH. We will first review more traditional therapies for PAH and their relevance in SSc-PAH, then discuss novel therapies for SSc-PAH. It will become apparent that, while similarities in pathogenesis exist between SSc-PAH and other forms of PAH, responses to therapy can widely differ for SSc-PAH.

General approach

Although limited data exist for either IPAH or SSc-PAH, consensus guidelines recommend the use of:

- supplemental oxygen in patients who are hypoxic at rest or with exercise (oxygen saturation < 90%);
- diuretics for the management of volume overload and in overt right heart failure;
- digoxin for management of refractory right heart failure complicated by atrial arrhythmias.

Calcium channel blockers

Although commonly used in patients with SSC for treatment of Raynaud’s phenomenon, there is little role for calcium channel blockers (CCB) in the treatment of SSc-PAH. Vasoreactivity is defined as a decrease in mean pulmonary arterial pressure by at least 20% and to less than 40 mmHg without a decline in CI or an increase in pulmonary capillary wedge pressure in response to a short-acting vasodilator such as inhaled nitric oxide. Currently, CCB are initiated in patients who have optimum vasoreactivity response while maintaining stable systolic blood pressure [122]. The commonly used agents are long-acting nifedipine, diltiazem or amiodipine. However, vasoreactivity is present in only a minority of patients with IPAH (~12%) and in approximately 1% of SSc-PAH patients [123]. Thus, high-dose CCB therapy for treatment of PAH is almost never indicated in SSc-PAH.

Anticoagulation

While evidence of pulmonary thromboembolic arterial disease and thrombosis in situ are often found in pathologic studies of patients with IPAH, there are few reports in the literature of similar findings in SSc-PAH [124]. Likewise, there are no data on the role of anticoagulation in the treatment of SSc-PAH. Several retrospective studies and one non-randomized prospective study have suggested improved outcomes in IPAH, while two retrospective studies suggested no clinical benefit [125]. A recent report by Olsson et al., from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) study group, demonstrated that the use of anticoagulation was associated with a survival benefit in patients with IPAH but not in patients with other forms of PAH [126]. Still, despite a lack of randomized controlled trials, consensus guidelines recommend anticoagulation for all IPAH patients and for patients with PAH related to connective tissue
diseases who have advanced disease [1]. While we encourage all of our SSc-PAH patients to begin oral anticoagulation, our experience in these patients suggests that less than 50% remain on long-term anticoagulation therapy. Bleeding is a major concern that necessitates cessation of anticoagulation therapy in patients with PAH. A recent study showed that the risk of bleeding differ among PAH subgroups [127]. The bleeding event rate was 5.4 per 100 patient-years for patients with IPAH and 19 per 100 patient-years for patients with connective tissue disease associated PAH.

Prostaglandins

Prostacyclin (epoprostenol) has proven effective in the management of PAH, demonstrating improvements in exercise capacity, cardiopulmonary hemodynamics, functional classification (New York Heart Association classification) and symptoms in patients with IPAH [128,129]. In fact, epoprostenol remains the only PAH-specific therapy to demonstrate a survival benefit in a randomized clinical trial [128]. In SSc-PAH, continuous intravenous epoprostenol improves exercise capacity and hemodynamics compared with conventional therapy, but does not improve survival [130]. Similar, albeit modest, responses to the prostacyclin analogue treprostinil, delivered through continuous subcutaneous infusion, were noted between IPAH and PAH related to connective tissue diseases (CTD-PAH) [131,132]. However, while functional capacity, exercise capacity, and hemodynamics improved in both IPAH and CTD-PAH, only half of the CTD-PAH group had SSc. Furthermore, the efficacy of treprostinil appears to be dose-related and the subcutaneous route of administration is often seriously limited by pain at the infusion site. Intravenous treprostinil is now approved by regulatory agencies for the treatment of PAH, including SSc-PAH. Although required maintenance doses are usually twice as high when compared with epoprostenol (affecting the cost of administration), the safety profile and drug stability offers some advantages [133]. Still, despite the potential efficacy of prostacyclin agents, the need for continuous infusion, meticulous catheter care and daily preparation of the medication can be challenging in patients whose manual dexterity may be impaired by significant Raynaud’s phenomenon, sclerodactyly and digital ulcerations. At our center, many SSc-PAH patients are unable to receive parenteral therapy as a result of these physical limitations. Although inhaled prostacyclin analogues have been developed for the treatment of PAH, no studies or specific subgroup analyses on efficacy of inhaled iloprost in SSc-PAH have been reported. The utility of inhaled iloprost is limited by the frequency with which the medication must be dosed; many patients are unable or unwilling to take the medication six- to nine-time daily as prescribed. Inhaled treprostinil is currently available in the US but not in Europe and requires less frequent dosing (four- to six-time daily). While demonstrating efficacy as add-on therapy with oral agents in a mixed cohort of PAH patients, subgroup analyses have not been reported [134]. However, these medications may be useful adjunct therapies in patients who are physically unable to maintain parenteral prostacyclin therapy.

Endothelin receptor antagonists

Treatment with bosentan, the first approved oral therapy for PAH, improves New York Heart Association functional class, 6MWT, time to clinical worsening and hemodynamics in PAH [135]. In a subgroup analysis of patients with SSc-PAH included in this initial study, there was a non-significant trend towards improvement in 6MWT in bosentan-treated patients compared with placebo. A 48-week, open-label study of patients with various forms of CTD, the majority of whom had SSc, demonstrated functional improvements in over 25% of these patients, while the 1-year survival was 92% [136]. However, no 6MWT was reported and quality of life, as assessed by the Short Form-36 and Health Assessment Questionnaire modified for SSc, did not improve. Our experience suggests that long-term outcome of SSc-PAH patients receiving bosentan as initial therapy is inferior compared with IPAH patients, with no improvement in functional class and poorer survival [137]. Still, guidelines from the European League against Rheumatism recommend bosentan as initial therapy for SSc-PAH based upon the quantity and quality of available data [138].

In an effort to target the vasoconstrictive effects of endothelin while preserving its vasodilatory action, selective endothelin-A receptor antagonists have been developed. Sitaxsentan, which had been approved in Europe for treatment of PAH, demonstrated exercise capacity, quality of life and hemodynamics in a post-hoc analysis of a randomized controlled trial that included patients with PAH-CTD [139]. This drug has since been removed from the market owing to significant hepatotoxicity and death. A large placebo-controlled, randomized trial of ambrisentan, the only currently FDA-approved selective endothelin receptor antagonist, improved 6MWT in PAH patients at week 12 of treatment; however, the effect was larger in IPAH compared with CTD-PAH patients (range: 50–60 vs 15–23 m, respectively) [140]. No other outcome measures (time to clinical worsening, change in functional class, quality of life, change in brain natriuretic peptide level or safety) were reported by PAH type. Furthermore, the proportion of CTD patients with SSc was not reported. Ambrisentan is generally well tolerated although peripheral edema (in up to 20% of patients) and congestive heart failure have been reported. Macitentan is a novel dual endothelin receptor antagonist that was approved by the FDA for treatment of PAH based on a recent clinical trial, which used as a primary endpoint the time from initiation of treatment to the first occurrence of a composite endpoint (death, atrial septostomy, lung transplantation, initiation of protonoids, or worsening PAH). Macitentan (added to background PAH therapy or placebo) significantly reduced
Importantly, the life expectancy of patients with PAH has been widely employed in the treatment of PAH. A larger clinical trial demonstrated improvement in 6MWT in subjects with various forms of PAH, including CTD-related disease [109]. A post-hoc analysis of the PAH-CTD subjects in the larger study found improvements in 6MWT, functional class and hemodynamics after 12 weeks of therapy with 20 mg three-time daily. No further improvements were noted in subjects who received either 40 mg three-time daily or 80 mg three-time daily doses. Importantly, less than 50% of the CTD patients in this study had SSC, thereby limiting the generalizability to SSC-PAH. Still, given the favorable safety profile, sildenafil is an attractive agent for initial therapy in SSC-PAH. The results of a large, randomized study of tadalafil, a once-daily phosphodiesterase inhibitor, demonstrate a significant improvement in 6MWT, time to clinical worsening and quality of life in subjects who received 40 mg daily [142]. Statistically significant improvements in 6MWT were also noted in the PAH-CTD group, although the proportion of patients with SSC was not reported. Importantly, over half of the participants were on therapy with bosentan 125 mg twice daily at enrollment, which may have impacted the magnitude of response to additional therapy with tadalafil. Thus, tadalafil may be a useful alternative to sildenafil in the treatment of SSC-PAH given its safety profile and once-daily administration. Regardless of the oral therapy selected as initial therapy, the effect upon exercise capacity may not be significant. As demonstrated in a systematic review of all randomized controlled trials evaluating the efficacy of bosentan, sitaxsentan and sildenafil, the effect size, defined as the ratio of the treatment effect (mean differences in 6MWT between treatment and placebo groups) to the pooled standard deviation of the differences, was small to moderate at best and not statistically significant for any drug studied [143]. While this study highlights the limited response in 6MWT to oral therapies in SSC-PAH, it also emphasizes the need for appropriate outcome measures in SSC-PAH as previously discussed.

**Soluble guanylate cyclase stimulator**

Riociguat, a novel drug recently approved by FDA, is a stimulator of soluble guanylate cyclase (sGC), a key enzyme in the nitric oxide signalling pathway. As such, riociguat constitutes the first drug of a novel class of sGC stimulators in the treatment of PAH. A recent phase III clinical trial demonstrated that riociguat significantly improved exercise capacity in patients with PAH [144]. By the end of the trial, 6MWD increased by a mean of 30 m in the 2.5 mg group (maximum dose group) and decreased by a mean of 6 m in the placebo group. The treatment effect was consistent in several patient subgroups, including CTD-PAH (~ 25% of the study population). The proportion of CTD patients with SSC, however, was not reported.

**Combination therapy**

Given the possible synergistic effects of the available PAH therapies that target separate pathways involved in the pathogenesis of the disease, combination therapy has become common practice in pulmonary hypertension centres. Several multicentre trials are now exploring the efficacy of various combinations of oral drugs, oral and inhaled drugs, and oral and intravenous drugs. The Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES) trial demonstrated that adding sildenafil at 80 mg three-time daily to intravenous epoprostenol improved exercise capacity, time to clinical worsening, quality of life and hemodynamics in patients with PAH [145]. However, while no subgroup analyses were reported, the improvement noted was mainly in IPAH subjects and in those whose exercise capacity was better at baseline. Furthermore, only 11% of the cohort had SSC-PAH. Therefore, whether addition of sildenafil to epoprostenol is efficacious in SSC-PAH remains uncertain.

As mentioned previously, a recent study of inhaled treprostinil as add-on therapy for PAH has demonstrated improvements in functional capacity and quality of life in a mixed cohort of PAH [134]. While over 30% of the study participants were designated as having collagen vascular disease, the proportion of patients with SSC was not reported. Furthermore, to date, no subgroup analyses have been published. We have found poorer response to a combination of oral therapies in SSC-PAH compared to IPAH [146]. While the addition of sildenafil to bosentan monotherapy improved 6MWT and functional class in IPAH subjects, SSC-PAH subjects did not experience significant improvement, although clinical deterioration may have been slowed in these patients. Importantly, there were significantly more side effects in SSC-PAH subjects compared with IPAH, including hepatotoxicity. Clinically important interactions between sildenafil and bosentan, including decreasing serum concentrations of sildenafil and increasing serum levels of bosentan, can occur when co-administered [147]. Whether these interactions are the same in SSC-PAH remains unknown; however, underlying gastrointestinal disorders such as esophageal dysmotility, gastraparesis, small bowel malabsorption and pancreatic insufficiency may interfere with drug absorption and metabolism.

**Novel therapies**

Recent discoveries that highlight the aberrant proliferation of endothelial and smooth muscle cells in PAH have prompted the
study of antineoplastic drugs initially in experimental models, and now in clinical trials. While a Phase II study of imatinib demonstrated significant improvements in hemodynamic measurements [148], and a Phase II study demonstrated improved exercise capacity and hemodynamics in patients with very advanced PAH, the latter trial was hindered by a number of subdural hematomas [149]. This drug will not be considered for approval by the regulatory agencies in the US or Europe.

Given the potential role of autoimmunity in the pathogenesis of SSc-PAH, therapies targeting B-cells are also being studied. Currently, a randomized clinical trial of rituximab, an anti-CD20 therapy that depletes B-cell lineages, is specifically and exclusively enrolling SSc-PAH patients who are already on concomitant PAH-specific therapy to assess hemodynamic response. Recently, the transcription factor Fos-related antigen-2 (Fra-2), a member of the activator protein 1 (AP-1) family implicated in TGF-β and PDGF signalling has been found to be highly expressed in patients with SSc [150]. Since transgenic overexpression of Fra-2 causes fibrosis and vascular disease (e.g., severe peripheral microangiopathy) [151], this factor may serve as a potential therapeutic target.

Lung transplantation
Despite the advances in medical therapy for PAH, lung transplantation remains the ultimate therapeutic option. Although CTD is not an absolute contraindication to lung transplantation, SSc patients tend to have multorgan disease that increases peri- and postoperative risk. In particular, esophageal dysmotility, common in SSc, may increase the risk of aspiration and post-transplant dysfunction. Clinical and subclinical renal disease may also increase the likelihood of complications related to the prolonged use of potentially nephrotoxic immunosuppressive agents. For these reasons, SSc-PAH patients are often denied lung transplantation. However, our experience shows that with proper screening, patients with SSc have similar rates of survival after lung transplantation compared with patients with pulmonary fibrosis or IPAH [152].

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PMH has served on an Advisory Board for Gilead for their research program. This activity has no relevance to the content of this manuscript.

MH has relationships with drug companies including Actelion, Bayer, GSK, Lilly, Novartis, and Pfizer. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards.

References
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