Published in final edited form as:

Heart Fail Clin. 2012 July ; 8(3): 413–425. doi:10.1016/j.hfc.2012.04.001.

Pulmonary Arterial Hypertension in Connective Tissue Diseases

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Keywords

connective tissue disease; pulmonary hypertension; scleroderma; systemic lupus erythematosus; mixed connective tissue disease; therapy

I. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease caused by a remodeling of precapillary arterioles that leads to a progressive increase in pulmonary vascular resistance and right ventricular failure. PAH is associated with significant morbidity and mortality, despite the advent of specific therapies that target pathobiologic pathways implicated in the disease process [1–3]. PAH can only be diagnosed by right heart catheterization (RHC) and is defined as a mean pulmonary artery pressure greater than 25 mmHg in the absence of elevation of the pulmonary capillary wedge pressure. PAH includes a heterogeneous group of clinical entities sharing similar pathological changes that have been subcategorized as idiopathic PAH (IPAH), familial PAH, and pulmonary hypertension associated with other diseases such as connective tissue diseases (CTD), portopulmonary hypertension and pulmonary hypertension related to HIV infection, drugs and toxins. An updated classification of all pulmonary hypertension syndromes from the 4th World Symposium held at Dana Point, California in 2008, has been recently published [4].

The exact mechanisms involved in the pathogenesis of PAH remain vastly unknown but are likely to involve significant alterations in endothelial function [5], an understanding of which has led over the past two decades to targeted therapy for this disease [6]. Several lines of evidence also support a role for autoimmunity in the development of the pulmonary vascular changes, including the presence of circulating autoantibodies [7], pro-inflammatory cytokines (e.g., IL-1 and IL-6) [8], and association of PAH with auto-immune diseases and CTD such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD). Despite the similarities in disease pathogenesis and hemodynamic perturbations, outcomes in patients with CTD-associated PAH differ significantly from other forms of PAH. In particular, SSc-associated PAH (SSc-PAH)

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The authors have nothing to disclose.

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patients have a poorer response to therapy and significantly worse survival compared to IPAH patients [9–11]. While there are serologic and pathologic features suggestive of inflammation in both IPAH and SSc-PAH, inflammatory pathways and autoimmunity are likely more pronounced in SSc-PAH, perhaps explaining clinical discrepancies between the two syndromes [9,10]. Other connective tissue diseases such as SLE, MCTD, and to a lesser extent rheumatoid arthritis (RA), dermatomyositis, and Sjogren's syndrome can also be complicated by PAH and will be discussed separately in this review.

II. Scleroderma

SSc is a heterogeneous disorder characterized by dysfunction of the endothelium, dysregulation of fibroblasts resulting in excessive production of collagen, and abnormalities of the immune system [12]. Progressive fibrosis of the skin and internal organs is a pathologic hallmark of the disease resulting in major organ damage and failure explaining the high morbidity and early death. Genetic and environmental factors are thought to contribute to host susceptibility [13] in the context of autoimmune dysregulation. Whether presenting in the limited or diffuse form, SSc is a systemic disease with the propensity to involve multiple organ systems such as the gastrointestinal tract, the heart, kidneys and lungs [14]. Pulmonary manifestations include PAH, interstitial fibrosis, and increased susceptibility to lung neoplasms.

The use of a standard classification system for SSc has allowed more accurate estimates of incidence and prevalence of SSc, which vary according to geographic location [15], supporting a role for environmental factors in disease pathogenesis. Prevalence of SSc ranges from 30–70 cases per million in Europe and Japan [16–18] to ~240 cases per million in the United States [15]. Incidence varies similarly by geographic area, with the highest rates found in the US (~19 persons per million per year) [19].

III. Scleroderma-associated PAH (SSc-PAH)

The prevalence of PAH in SSc patients, when the diagnosis is based on right heart catheterization for assessment of filling pressures, is about 8–14% [20,21]. Previous assessments based on echocardiographic measurements [22–25] have overestimated the true prevalence of SSc-PAH and should not be relied upon for establishing the diagnosis and initiating treatment. Echocardiography is limited in the diagnosis of PAH due to the inaccuracy of the Doppler signal in assessing true right ventricular systolic pressure [26] and the frequent inability to obtain an adequate Doppler signal, particularly in patients with CTD {Murata, 1992 #251}. Further, if estimated right ventricular pressure is indeed elevated, other diagnoses such as pulmonary venous hypertension cannot be excluded with certainty by echocardiography. However, while echocardiography overestimates the prevalence of PAH due to misclassification, it is likely that SSc-PAH remains overall under-diagnosed as suggested by the lower than expected prevalence of the disease in the few registries available [27–29].

a. Pathophysiology

There are early vascular changes in SSc [30] which include gaps between endothelial cells [31], cellular apoptosis [32], endothelial activation with expression of cell adhesion molecules, inflammatory cell recruitment, a procoagulant state [33], and remodeling of the small vessels with intimal proliferation and adventitial fibrosis leading to vessel obliteration. The extent of these vascular lesions in vital organs such as the lungs, kidneys and heart defines the prognosis of patients with SSc [34].

Specific endothelial injury is reflected by increased levels of soluble vascular cell adhesion molecule (sVCAM-1) [35], disturbances in angiogenesis reflected by increased levels of circulating vascular endothelial growth factor (VEGF) [36,37] and presence of angiostatic factors [36,38]. Increased VEGF may be a consequence of increased angiogenesis or profound disturbances in signaling in SSc. Dysregulated angiogenesis in SSc-PAH, exemplified by the up-regulation of VEGF a glycoprotein with potent angiogenic and vascular permeability-enhancing properties, is a predominant pathological feature of the disease and is a logical candidate for therapeutic targeting.

b. Autoantibodies

Several antibodies are frequently found in SSc-PAH such as antifibrillar antibodies (anti-U3-RNP) [39] and the poorly characterized anti-endothelial antibodies (aECA) which correlate with digital infarcts [40]. Antibodies to fibrin-bound tissue plasminogen activator in CREST patients [41] and in IPAH patients with HLA-DQ7 antigen [42], and anti-topoisomerase II- α antibodies, particularly in association with HLA-B35 antigen [43], have been reported in SSc-PAH. aECA antibodies which can activate endothelial cells, induce the expression of adhesion molecules, and trigger apoptosis, are thought to play a role in the pathogenesis of PAH [44].

Fibroblasts are essential components of the pulmonary vascular wall remodeling in PAH and are found in the remodeled neointimal layer in both SSc-PAH and IPAH. In that regard, the detection of anti-fibroblast antibodies in the serum of SSc and IPAH patients [45,46] has significant pathogenic importance since these antibodies can activate fibroblasts and induce collagen synthesis, thus contributing potentially directly to the remodeling process. Antibodies from sera of patients with SSc induce a pro-adhesive and pro-inflammatory response in normal fibroblasts [46]. Antifibroblast antibodies from sera of IPAH and SSc-PAH patients have distinct reactivity profiles [47] and react with fibroblast proteins involved in regulation of cytoskeletal function, cell contraction, cell and oxidative stress, cell energy metabolism and in different key cellular pathway [48].

Taken together, particularly in light of the positive response to immunosuppressive therapy for some patients with PAH associated with SLE and MCTD [49], these studies suggest that inflammation and autoimmunity play a major role in the pathogenesis of PAH, perhaps more specifically in CTD-associated PAH.

c. Genetic factors

Polymorphisms involving the bone morphogenetic protein receptor-2 (*BMPRII*) are present in over 80% of familial IPAH [50,51] and up to 25% of sporadic [52,53] cases of IPAH. Additional candidate genes have been proposed to influence the pathogenesis of PAH [54]. Polymorphisms of the activin-receptor-like kinase 1 (*ALK1*) gene, another member of the TGF β receptor superfamily, have been reported in patients with hereditary hemorrhagic telangiectasia (HHT) and PAH [55]. However, to date *BMPR2* mutations have not been identified in two small cohorts of SSc-PAH patients [56,57].

Candidate genes associated with SSc have been reported in different populations and include a variant in the promoter of monocyte chemotactic protein-1 (MCP-1) [58]; two variants in CD19 (-499G>T and a GT repeat polymorphism in the 3'-UTR region) [59]; a promoter and coding polymorphism in TNFA (TNFA-238A>G, TNFA 489A>G) [60]; a variant in the promoter of the IL-1 α gene (IL1A -889T) [61,62]; and a 3-SNP haplotype in IL10 [63]. A genome-wide association analysis provided evidence for association to multiple loci in a Native American population [64].

Recently, an association between an endoglin gene (*ENG*) polymorphism and SSc-related PAH was identified. Wipf and colleagues demonstrated a significant lower frequency of the 6bINS allele in SSc-PAH patients as compared to controls or patients with SSc but no PAH [65]. Endoglin, a homodimeric membrane glycoprotein primarily present on human vascular endothelium, is part of the TGF- β receptor complex. The functional significance of the *ENG* polymorphism in SSc patients remains to be determined.

Thus, there is compelling data supporting a genetic basis for SSc. However, aside from the few examples cited above, the genes relevant to the pathogenesis and poor outcome associated with SSc-PAH have not been identified, and their definition will require robust, well-characterized large patient populations to provide adequate power for analysis.

d. Clinical features

Risk factors for the development of PAH in SSc patients include late-onset disease [66], an isolated reduction in DLCO, an FVC%/DLCO% ratio greater than 1.6 [67,68], or a combined decreased DLCO/alveolar volume with elevation of serum N-terminal pro-brain natriuretic peptide levels [69]{Shah, #642}{Negi, 1998 #164}, among others. (Table 1). Typically, patients with SSc-PAH are predominantly women, have limited sclerosis with predominantly anticentromere antibodies, are older and have seemingly less severe hemodynamic impairment compared to IPAH patients [10]. Clinical symptoms are non specific, including dyspnea, functional limitation which may be more severe than in IPAH due not only to older age but also to frequent involvement of the musculoskeletal system in these patients. SSc-PAH patients also tend to have other organ involvement such as renal dysfunction and intrinsic heart disease. Indeed patients with SSc (even in the absence of PAH) tend to have depressed RV function [70,71] as well as left ventricular systolic and diastolic dysfunction [72]. Like IPAH patients, SSc-PAH patients have severe RV dysfunction already at time of presentation but have more severely depressed RV contractility compared to IPAH patients [73]. In addition, SSc-PAH patients are more likely to have LV diastolic dysfunction and pericardial effusion (34% compared to 13% for IPAH) [10]. In both groups, pericardial effusion portends a particularly poor prognosis [10].

SSc-PAH patients also tend to have more severe hormonal and metabolic dysfunction such as high levels of N-terminal brain natriuretic peptide (N-TproBNP) [74] and hyponatremia [75]. Both N-TproBNP and hyponatremia have been shown, at baseline and with serial changes (for N-TproBNP [74]), to correlate with survival in PAH [74,75].

e. Early Detection

While IPAH is usually diagnosed late (patients presenting in WHO functional status III and IV), a population at risk for PAH such as SSc theoretically allows establishing measures for early detection. An algorithm for early detection of PAH may be helpful if based on a combination of symptoms and screening echocardiography (Figure 1) as exemplified by a recent large French registry where patients with SSc with tricuspid regurgitation velocity (TRV) jet by transthoracic echocardiography greater than 3 m/sec or between 2.5 and 3 m/sec if accompanied by unexplained dyspnea, were systematically referred for right heart catheterization [20]. Investigators were able to detect incident cases of SSc-PAH with less severe disease (as judged on hemodynamic data) compared to patients with known disease. Therefore, unexplained dyspnea should prompt a search for PAH in these patients, in particular in the setting of a low single breath DLCO or declining DLCO over time [68], echocardiographic findings suggestive of the disease (elevated TRV jet or dilated RV or right atrium), or elevated levels of N-TproBNP which can reflect cardiac dysfunction and have been found to predict the presence of SSc-PAH [74]. Systematic screening should

allow detection of early disease and prompt therapy which may theoretically be beneficial from a prognostic standpoint [76].

f. Prognosis

Patients with SSc-PAH have a worse prognosis compared to patients with other forms of PAH such as IPAH. Indeed, one-year survival rates for SSc-PAH patients range from 50–1% [9,11,21,25,77], considerably lower than the estimated 88% one year survival for IPAH patients [78]. Even when compared to patients with other forms of CTD-PAH, survival is markedly reduced in SSc-PAH. (Figure 2) In all patients with SSc, PAH significantly worsens survival and is one of the leading causes of mortality in these patients [15,77,79].

IV. PAH associated with other connective tissue diseases

PAH can complicate any connective tissue disease, most frequently SSc as discussed above, but also SLE, MCTD, RA, or other diseases such as Sjogren's syndrome and dermatomyositis.

a. Systemic lupus erythematosus

Pulmonary vascular involvement is common in SLE and, like in SSc, there is evidence of endothelial dysfunction with an imbalance between vasodilators and vasoconstrictors. Endothelin levels are high in patients with SLE, particularly in those patients with pulmonary hypertension. Other factors contributing to pulmonary vascular derangement in SLE include recurrent thromboembolic disease, particularly in patients with a hypercoagulable state from antiphospholipid antibodies which are present in up to 10% of patients with SLE [80], pulmonary vasculitis, and parenchymal disease (e.g., interstitial lung disease, and the shrinking lung syndrome from myositis of the diaphragm). Combined vasculitis and chronic hypoxia are frequent contributing offenders in these syndromes. Finally, pulmonary venous hypertension may be a consequence of left ventricular dysfunction, myocarditis, or Libman Sachs endocarditis.

The prevalence of PAH in SLE is unclear but is likely less than in SSc, affecting about 0.5–14% patients with SLE in a large review of the literature encompassing over 100 patients [81]. The patients are predominantly female (90%), young (average age of 33 at time of diagnosis), and often suffer from Raynaud's phenomenon. The pathological lesions are often indistinguishable from IPAH or SSc-PAH lesions, with intimal hyperplasia, smooth muscle cell hypertrophy, and medial thickening. Survival, which was quite poor (25–50% at 2 years) even compared to SSc-PAH in studies antedating specific PAH therapy, is now improved and estimated at 75% [11]. It is also better than in SSc-PAH (Figure 2).

b. Mixed connective tissue disease

Patients with MCTD have clinical features which overlap between those of SSc, SLE, RA, and polymyositis. The exact prevalence of PAH in MCTD is unknown but is thought to be as high as 50% [82]. PAH in these patients may occasionally respond to immunosuppressive drugs [49].

c. Rheumatoid arthritis

Both the prevalence and impact of PAH in patients with RA have not been well characterized but are thought to be relatively low compared to other CTD such as SSc, SLE and MCTD.

d. Primary Sjogren's syndrome

Although primary Sjogren's syndrome (pSS) is a relatively common autoimmune disease with glandular and extraglandular manifestations, it is very rarely complicated by PAH. In a recent review by Launay et al of patients with pSS and PAH [83], the mean age at diagnosis of PAH of these almost exclusively female patients was 50 years. Patients had severe functional class (FC III and IV) and hemodynamic impairment. Standard therapy (with endothelin receptor antagonists, phosphodiesterase inhibitors or prostanoids) was typically ineffective despite an initial improvement. Some patients were reported to respond to immunosuppressive treatment. However, any conclusion regarding treatment is limited by the small size of this case report. Survival rate was low (66% at 3 years).

V. Therapy for PAH related to CTD

While randomized, clinical trials of novel therapeutics for the treatment of PAH have included patients with PAH associated with CTD, the majority of these subjects included in trials were SSc-PAH. Given the differences in survival and potential differences in response to immunosuppressive therapy between the various forms of CTD associated PAH, the generalizability of the results of the clinical trials may be limited to only SSc-PAH. However, the therapies discussed below are commonly used in all forms of CTD-associated PAH, though the evidence base for diseases other than SSc is lacking.

Evidence of chronically impaired endothelial function [84–86], affecting vascular tone and remodeling, is the basis for current PAH therapy. Vasodilator therapy using high dose calcium channel blockers [87] is an effective long-term therapy for a minority of patients with IPAH who demonstrate acute and sustained vasodilation (*e.g.*, to NO or adenosine) during hemodynamic testing [88]. However, since most patients with CTD-associated PAH patients fail to demonstrate a vasodilator response to acute testing [27], high dose calcium channel therapy is usually not indicated for these patients except at low dosage for Raynaud's syndrome. Further, because the proportion of CTD patients who demonstrate a positive vasodilator response is so low, current guidelines recommend vasodilator testing be performed on an individual basis in patients with CTD-associated PAH {McLaughlin, 2009 #733}.

a. Anti-inflammatory drugs

Inflammation may play a significant role in PAH associated with CTD. In that respect, it is interesting to note that occasional patients with severe PAH associated with some forms of CTD (such as SLE, primary Sjögren syndrome, and MCTD) have had dramatic improvement of their pulmonary vascular disease with corticosteroids and/or immunosuppressive therapy [49]. Unfortunately, this has not been the case for patients with SSc-PAH whose PAH is usually notoriously refractory to immunosuppressive drugs [49].

b. Prostaglandins

Prostacyclin (epoprostenol) has potent pulmonary vasodilator, anti-platelet aggregating and antiproliferative properties [89], and has proven effective in improving exercise capacity, cardiopulmonary hemodynamics, NYHA functional class, symptoms, as well as survival in patients with PAH when given by continuous infusion [90–92]. In SSc-PAH, continuous intravenous epoprostenol improves exercise capacity and hemodynamics [93], compared to conventional therapy, and may have long-term beneficial effects [94] although a clear effect on survival in these patients there has yet to be demonstrated.

Treprostinil, an analogue of epoprostenol suitable for continuous subcutaneous administration, has modest effects on symptoms and hemodynamics in PAH [95]. In a small

study of 16 patients (among whom 6 had connective tissue disease related PAH), intravenous treprostinil improved hemodynamics 6 minute walk distance (6MWD), functional class (FC), and hemodynamics after 12 weeks of therapy [96]. Although the safety profile of this drug is similar to IV epoprostenol, required maintenance doses are usually twice as much as for epoprostenol. However, for patients with SSc-PAH and often severe and debilitating Raynaud's phenomenon, the lack of requirement of ice packing and less frequent mixing of the drug offer significant advantages.

Several reports of pulmonary edema in SSc-PAH patients treated with prostaglandin derivatives, both in acute and chronic settings, have raised the suspicion of increased prevalence of veno-occlusive disease in these patients [97,98], and concern about usefulness of these drugs for this entity. Nevertheless, intravenous prostaglandin therapy remains an option for patients with CTD-PAH with NYHA class IV. Considering the frequent digital problems and disabilities that these patients often experience, this form of therapy can be quite challenging and may increase the already heavy burden of disease in these patients. In summary, both epoprostenol and treprostinil are FDA approved for PAH, but are cumbersome therapies requiring continuous parenteral administration with the attendant numerous adverse effects (*e.g.*, infection and possibility of pump failure [99]), which make these drugs less than ideal.

c. Endothelin receptor antagonists

In randomized, placebo-controlled trials bosentan therapy was shown to have a beneficial effect on functional class, 6-minute walk distance, time to clinical worsening and hemodynamics in PAH [100,101]. Roughly one fifth of these patients consisted of SSc-PAH patients while a large majority had a diagnosis of IPAH. In a subgroup analysis, there was a non-significant trend towards a positive treatment effect on 6MWD among the SSc-PAH patients treated with bosentan compared to placebo [101]. At most, bosentan therapy prevented deterioration in these patients. Reasons for the less than optimal effect of therapy in patients with SSc-PAH are unknown but may be related to the severity of PAH at time of presentation, as well as other factors such as potentially more severe RV and pulmonary vascular dysfunction compared to patients with other forms of PAH (*e.g.*, IPAH).

In a recent analysis of patients with CTD-PAH (*e.g.*, patients with lupus, overlap syndrome, and other rheumatologic disorders) included in randomized clinical trials of bosentan, there was a trend toward improvement in 6 MWD and improved survival compared to historical cohorts [102]. Single center experience suggests that long-term outcome of first-line bosentan monotherapy is inferior in SSc-PAH compared to IPAH patients, with no change in FC and worse survival in the former group [103]. Since ET-1 appears to play an important pathogenic role in the development of SSc-PAH, contributing to vascular damage and fibrosis, inhibiting ET-1 remains a rational therapeutic strategy in these patients. As an example of mechanistic effect, in a small study of 35 patients with SSc (10 of whom had SSc-PAH), bosentan treatment appeared to reduce endothelial cell (as determined by endothelial soluble serum factors such as ICAM-1, VCAM-1, P-selection and PECAM-1) and T cell subset (assessed by expression of lymphocyte function-associated antigen-1, very late antigen-4, and L-selectin on CD3 Tcells) activation [104]. Aside from improving pulmonary hypertension, ET-1 receptor antagonists (specifically bosentan) cause significant reductions in the occurrence of new digital ulcerations; however, preexisting ulcers do not seem to improve with this therapy [105].

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 RCT that

included 42 patients with CTD-PAH [Girgis, 2007 #584]. However, recently, this drug was removed from the market due to significant hepatotoxicity and death. A large placebo-controlled, randomized trial of ambrisentan, the only currently FDA-approved selective endothelin receptor antagonist, improved 6MWD in PAH patients at week 12 of treatment, however, the effect was larger in patients with IPAH compared to patients with CTD-PAH (range of 50–60 meters versus 15–23 meters, respectively)[106]. Ambrisentan is generally well tolerated although peripheral edema (in up to 20% of patients [106]) and congestive heart failure have been reported.

d. Phosphodiesterase inhibitors

Sildenafil, a phosphodiesterase type V inhibitor that reduces the catabolism of cGMP, thereby enhancing the cellular effects mediated by nitric oxide, has become a widely used and highly efficacious therapy for PAH. The pivotal SUPER trial demonstrated that sildenafil therapy improved 6 MWD in patients with IPAH, CTD-PAH, or PA associated with repaired congenital heart disease (patients were predominantly FC II or III) at all three doses tested (20, 40, and 80 mg, given three times a day) [107]. The current FDA-recommended dose is 20 mgs three times a day since there were no significant differences in clinical effects and time to clinical worsening at week 12 between all doses tested. In a post-hoc subgroup analysis of 84 patients with PAH related to CTD (forty-five percent of whom had SSc-PAH), data from the SUPER study suggest that sildenafil at a dose of 20 mgs improved exercise capacity (6 MWD), hemodynamic measures and functional class after 12 weeks of therapy [108]. However, there was no effect for the dose of 80 mgs three times a day on hemodynamics in this subgroup of patients with CTD-related PAH [108]. For this reason and because of the potential of increased side-effects (such as bleeding from arterio-venous malformations) at high doses, a sildenafil dosage of 20 mgs three times a day is recommended for SSc-PAH patients (and patients with PAH associated with other forms of CTD) as standard therapy. Higher doses are occasionally attempted in case of limited response. The impact of long-term sildenafil therapy on survival in these patients remains to be determined. Finally, tadalafil, another phosphodiesterase inhibitor, has now been shown to be effective for PAH [109] although subgroup analysis has not been performed yet and thus its effects on CTD-PAH remain unclear. Tadalafil has the advantage over sildenafil of single daily dosage.

e. Combination therapy

It is now common practice to add drugs when patients fail to improve on monotherapy. Adding inhaled iloprost to patients receiving bosentan has been shown to be beneficial in a small, randomized trial. Combining inhaled iloprost with sildenafil is mechanistically appealing and anecdotally efficacious [110,111] as these drugs target separate, potentially synergistic pathways. Several multicenter trials are now exploring the efficacy of various combinations of two oral drugs or one oral and one inhaled drug. The recently published results of the PACES trial demonstrate that adding sildenafil (at a dose of 80 mgs three times a day) to intravenous epoprostenol improves exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life [112]. About 21% of these patients had CTD, including 11% with SSc-PAH. Although no specific subgroup analysis is provided, improvement was apparently mainly in patients with IPAH. In a smaller one center clinical trial, adding sildenafil to patients with IPAH or scleroderma-related PAH after they failed initial monotherapy with bosentan, demonstrates that combination therapy improved the 6MWD and FC in IPAH patients. The outcome in patients with SSc-PAH was less favorable, although combination therapy may have halted clinical deterioration. In addition, there were more side-effects reported in the SSc-PAH compared to the IPAH patients, including hepatotoxicity that developed after addition of sildenafil to bosentan monotherapy [113].

f. Anticoagulation

Based essentially on retrospective data showing a survival advantage [87,114], anticoagulation is routinely recommended in the treatment of IPAH patients. However, the role of anticoagulation in other forms of PAH, in particular in CTD-PAH is much less clear. Theoretically, there is potential for increased bleeding in patients with CTD, particularly with SSc where intestinal telangiectasias may be common. In our experience, less than 50% of SSc-PAH patients started on anticoagulation remain on therapy long-term because of bleeding complications (e.g., often related to occult bleeding in the gastrointestinal tract) which are often difficult to diagnose.

g. Tyrosine kinase inhibitors

The finding that there is pathologically aberrant proliferation of endothelial and smooth muscle cells in PAH, as well increased expression of secreted growth factors such as VEGF and bFGF, has caused a shift in paradigm in treatment strategies for this disease as some investigators have likened this condition to a neoplastic process reminiscent of advanced solid tumors [115]. As a result, anti-neoplastic drugs have been tested in experimental models [116,117]. The results of a phase II multicenter trial to evaluate the safety, tolerability, and efficacy of this drug in patients with PAH have recently published and indicate that imatinib is well tolerated in PAH patients. While there was no significant change in 6 minute walk distance (primary end-point) there was a significant decrease in pulmonary vascular resistance and an increase in cardiac output in imatinib-treated patients versus placebo [118]. Whether these new anti-neoplastic drugs with anti-tyrosine kinase activity will have a role in SSc (where there is evidence for both dysregulated proliferation and increased expression of growth factors such as VEGF [119]) or in IPAH remains to be determined. Interestingly, a single case report suggests significant improvement of right ventricular function with imatinib treatment in a SSc-PAH patient. Also of note is that imatinib is being investigated for SSc-related interstitial lung disease [120].

h. Lung transplantation

Lung transplantation (LT) is typically offered as a last resort to patients with PAH who fail medical therapy. CTD is not an absolute contraindication to LT; however, patients with CTD-PAH frequently suffer from associated morbidity and organ dysfunction other than the lung, which places them at a significantly increased risk for LT. Motility disorder of the esophagus and gastroesophageal reflux in patients with SSc significantly enhance the postoperative potential of aspiration and damage to the recipient lung. For these reasons, patients with SSc-PAH are often denied LT consideration. However, if properly screened and approved for LT, patients with SSc experience similar rates of survival 2 years after the procedure compared with patients who receive LT for pulmonary fibrosis or IPAH [121]. In addition, a recent retrospective study suggests that the 1-year survival rate is similar for SSc patients (transplanted for respiratory failure related to PAH or interstitial lung disease) compared to patients with IPF although acute rejection appears to be more common for the former group [122].

VI. Conclusion

In summary, pulmonary hypertension is a common complication of CTD, particularly SSc where it carries a very poor prognosis. Despite modern therapy for PAH, survival of patients with CTD-PAH remains unacceptably low. Possible reasons include an increased prevalence of pulmonary veno-occlusive lung disease in SSc-PAH patients [123], or more severe vascular lesions affecting not only proximal and distal pulmonary vessels but also the heart (such as inflammatory myocarditis) in CTD. Thus, a better understanding of the underlying pathophysiology affecting the heart and pulmonary vessels in CTD is needed for better

targeted therapy. Whether specific anti-inflammatory agents or drugs targeting tyrosine kinase activity will have any role in CTD-PAH is unclear at this time but needs to be explored.

Acknowledgments

Supported by: NHLBI K23 HL092287 (SCM) and P50 HL084946 (PMH)

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Synopsis

Pulmonary arterial hypertension (PAH) may complicate diverse connective tissue diseases (CTD) such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and rheumatoid arthritis (RA), among others. Approximately 10% of patients with SSc will develop PAH; the prevalence is much lower in the other CTD. However, PAH is an important contributor to morbidity and mortality in all forms of CTD. Despite similarities in clinical presentation, hemodynamic perturbations, and pathogenesis, patients with CTD associated PAH (CTD-PAH) usually have a poorer response to PAH-specific medications and a poorer prognosis than patients with idiopathic PAH (IPAH). Similarly, while select patients with CTD-PAH may be candidates for lung transplantation, the results are less favorable than for IPAH due to co-morbidities and complications specifically associated with CTD. Future research focusing on the specific vascular and cardiac abnormalities in CTD-PAH is imperative to develop novel, targeted treatment.

1. Pulmonary arterial hypertension (PAH) is a common complication of connective tissue diseases (CTD) particularly scleroderma
2. When complicating CTD PAH significantly worsens survival and is a leading cause of death in these patients
3. Scleroderma-associated PAH carries a significantly worse prognosis compared to other forms of PAH such as idiopathic PAH (IPAH)
4. Standard PAH-specific therapy is not as effective in CTD-associated PAH compared to IPAH
5. There is a need for a better understanding of underlying mechanisms of CTD-associated PAH in order to design targeted therapy.

Figure 1. Algorithm for Detection of PAH in Patients with Systemic Sclerosis

Algorithm showing routine clinical tests in patients with systemic sclerosis aimed at early detection of pulmonary arterial hypertension or other causes of cardiac dysfunction (e.g., left ventricular dysfunction)

Abbreviations: PFTs-Pulmonary function tests; DLCO-single breath diffusing capacity to carbon monoxide; FVC-forced vital capacity; RV-right ventricle; TRV-tricuspid regurgitation jet; RHC-right heart catheterization.

Table 1

Clinical Risk Factors for the Development of PAH in Systemic Sclerosis

Limited SSc
Late age of onset of SSc
Raynaud's Phenomenon
Number of Telangiectasias
Decreased DL _{CO}
FVC %: DL _{CO} % > 1.6
Increased NT-proBNP
Antibodies (e.g. anti-U3 RNP)