Chapter 3
Beyond Scleroderma: Pulmonary Arterial Hypertension in Patients with Other Connective Tissue Diseases

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Introduction

Pulmonary hypertension (PH) describes a collection of clinical groups all characterized by abnormal elevation of pressures in the pulmonary circulation. Pulmonary arterial hypertension (PAH), or Group 1 PH, is a rare PH subgroup characterized by increased pulmonary vascular resistance, severe vascular remodeling, endothelial dysfunction, complex vascular lesions, and dysregulation of the innate and adaptive immune system [1]. The distinction between PAH and other PH subgroups is important, as PAH has the potential to progress rapidly, resulting in significant morbidity and mortality due to right heart failure. Furthermore, modern treatment options designed to decrease pulmonary vascular resistance are limited for use in patients with PAH.

The presence of PH in the setting of connective tissue disease (CTD) is an important consideration for clinicians as many CTD patients develop complications that predispose them to the development of PH. The challenge is that not all CTDs predispose patients to the same PH subgroups to the same frequency. For example, patients with rheumatoid arthritis and systemic sclerosis have an increased frequency of Group 2 PH secondary to left heart disease (such as diastolic dysfunction or valvular disease) while the frequency is less clear in patients with dermatomyositis, polymyositis, and eosinophilic granulomatosis with polyangiitis [2]. Group 3 PH secondary to lung disease and hypoxia is more frequent in patients with

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sarcoidosis, dermatomyositis, polymyositis, and systemic sclerosis [2]. Patients with antiphospholipid syndrome and systemic lupus erythematosus have an increased frequency of Group 4 PH due to chronic thromboembolic disease [2], while Group 5 PH (PH due to unclear and/or multifactorial mechanisms) is more frequent in patients with sarcoidosis and possibly systemic sclerosis [2]. The frequency of Group 1 PAH associated with CTD (CTD-PAH) is also know to vary by CTD subtype [3]. Thus, regional differences in CTD subtypes greatly affect the prevalence of CTD-PAH, with notable differences between Eastern and Western countries [3, 4]. Given its potential for rapid progression and high mortality, as well as advances in effective, disease-specific treatment options that may alter its natural history, great emphasis has been placed upon better understanding the global burden of CTD-PAH. Research efforts over the previous decade targeting the pathobiology, epidemiology, natural history, early diagnosis, and treatment of PAH associated with the scleroderma spectrum of disease (SSc-PAH) have been especially productive and serve as a guide for better understanding PAH associated with CTDs other than, or beyond, scleroderma.

Epidemiology of CTD-PAH

Historically, much of what is known about the prevalence of CTD-PAH is based upon retrospective and registry-based studies performed in the Western world. It is now appreciated that the prevalence of specific CTD subtypes, and thus the prevalence of CTD-PAH, may differ in the Eastern world. Group 1 pulmonary arterial hypertension (PAH) is estimated to have a prevalence of 15 cases per one million people in the Western world [5]. PAH associated with connective tissue diseases accounts for 15–25% of PAH [3, 5, 6]. Among connective tissue diseases, systemic sclerosis comprises the largest subgroup of CTD-PAH, accounting for 62–76% of cases in the United States and Europe [3, 5, 7]. The prevalence of PAH in systemic sclerosis has been estimated to be 7–12% [8–10].

Scleroderma

While systemic sclerosis is the most common cause of CTD-PAH in the Western world, this does not hold true in Asian-Pacific countries. A study examining Chinese patients with CTD-PAH found systemic lupus erythematous to be the most common cause of CTD-PAH, accounting for 59% of cases, followed by systemic sclerosis [4]. This predominance of systemic lupus erythematous has also been shown in Japan and Korea [11, 12]. In registries from the United States and France, SLE accounts for 7% and 19% of CTD-PAH, respectively [3, 5]. The prevalence of PAH in SLE is estimated to be 0.5–17.5% although a prevalence of up to 43% has previously been reported [13, 14]. It is important to note that the wide variation in

reported prevalence of CTD-PAH may be at least partially explained by the fact that echocardiographic parameters were used in several studies to diagnose PAH as opposed to the gold standard right heart catheterization [15]. This variability emphasizes the importance of using invasive hemodynamics to define CTD-PAH in future epidemiologic studies.

Mixed Connective Tissue Disease

US, French, and Chinese registries have shown mixed connective tissue disease to account for roughly 9% of CTD-PAH [3–5]. Whereas prior hospital-based studies have shown a prevalence of PAH among patients with mixed connective tissue disease ranging from 17% to 29%, a more recent Norwegian registry suggests a much lower prevalence [16–19]. Gunnarsson et al. followed an unselected cohort of 147 MCTD patients for 5.6 years and found PAH confirmed by right heart catheterization in approximately 3% of patients [19]. Changes in diagnostic criteria for MCTD and PAH and differences in the examined patient populations, including the fact that the earlier studies examined MCTD patients referred to tertiary centers, could partially account for the differences in prevalence.

Other Connective Tissue Diseases

Connective tissue diseases such as rheumatoid arthritis (RA), Sjögren's syndrome, and inflammatory myopathies have been less frequently associated with PAH. In the American REVEAL and Korean REOPARD registries, PAH associated with RA made up 8–9% of CTD-PAH patients [3, 20]. However, the prevalence of RA in the French PH Registry was found to be 0.35% (0.58% in idiopathic PAH), similar to the general French population and unsupportive of a strong association between RA and pulmonary arterial hypertension [21].

The prevalence of PAH in Sjögren's syndrome is rare and, up until recently, had only been reported in case reports. In Chinese registries, it has been found to account for 15–16% of CTD-PAH cases [4, 22]. Compared to Sjögren's syndrome in the absence of PAH, Sjögren's syndrome-associated PAH has been associated with Raynaud's phenomena and positive rheumatoid factor [23, 24].

There have been rare reports of patients with inflammatory myopathies, such as dermatomyositis and polymyositis, with PAH. In most cases, however, other causes of pulmonary hypertension, often due to lung involvement in these disease entities, and the presence of other connective tissue diseases due to overlap could not be completely excluded [25, 26] [27]. A study looking at the French PH registry showed PAH may be associated with dermatomyositis, skin involvement, peripheral microangiopathy, and anti-SSA positivity, though this was based on 3 out of a total of 5223 patients [28].

Similar to SSc-PAH, PAH associated with other connective tissue diseases appears to be more common in females [29]. Also, patients with SSc-PAH appear to fair worse than those with other types of CTD-PAH; one-year survival rates in PAH associated with scleroderma are poorer at 82% compared to 94% in SLE, 88% in MCTD, and 96% in RA [29].

Screening and Early Detection of CTD-PAH

Validated screening and accurate early detection are critical to the continued improvement in management of CTD-PAH. Often, patients with CTD are not diagnosed with PAH until relatively late in their clinical course [17, 30]. Given the influence of CTD-PAH on morbidity and mortality in patients with CTD, emphasis has been placed upon the development of screening protocols for CTD patients. The strongest evidence for formalized screening for early PAH is in the scleroderma spectrum diseases [31], where early diagnosis and treatment of SSc-PAH has been shown to improve outcomes [32]. Current guidelines emphasize annual screening in patients with SSc and SSc spectrum diseases (SSc, mixed CTD, or other CTDs with prominent scleroderma features such as sclerodactyly, nail fold capillary abnormalities, and SSc-specific antibodies) with an uncorrected diffusing capacity for carbon monoxide (DLCO) <80% of predicted [31]. Sufficient data to support standardized screening for PAH in other CTDs is currently lacking, but the current state of screening for, and early detection of, CTD-PAH is reviewed here.

Scleroderma Spectrum Diseases

PAH in patients with SSc is a major contributor to mortality, with an estimated 81% and 52% 1- and 3-year survival time for those diagnosed with SSc-PAH [33]. Disease severity at the time of diagnosis is recognized as largely responsible for poor prognosis [34–36]. Among those diagnosed with SSc-PAH, 79% are World Health Organization functional class III or IV at the time of diagnosis [34]. It is now recognized that formalized early detection programs for SSc-PAH identify milder forms of the disease, allowing for early treatment and improved long-term survival [32]. Since this landmark study, early detection programs have been developed for SSc-PAH. DETECT was a prospective, multinational study which evaluated the performance of an SSc-PAH early detection algorithm for patients with SSc of at least 3 years duration and a DLCO <60%. DETECT's two-step approach utilizes noninvasive biomarkers including the ratio of FVC % predicted to DLCO % predicted, telangiectasias (current/past), anticentromere antibody (ACA), serum NT-proBNP, serum urate, and electrocardiographic evidence right axis deviation. If patients meet a threshold based upon their cumulative score from the aforementioned biomarkers, the algorithm indicates the need for echocardiography (Step 1).

Based upon the right atrium area and TR velocity from echocardiography, a second risk score is calculated and patients who have a second threshold are referred for right heart catheterization (Step 2) [37]. In the original study, the DETECT algorithm referred 62% of patients for RHC, which definitely diagnosed SSc-PAH in 35% of those referred. Importantly, PAH was missed in only 4% of patients referred for RHC based upon the DETECT algorithm; 29% of PAH was missed in patients referred for RHC based upon the 2009 ESC/ESR screening recommendations [37]. Of note, the DETECT study was carried out in high-risk SSc patients, and less is known about early detection of, and screening for, PAH in low- or medium-risk SSc patients. Current evidence suggests, however, that the DETECT algorithm is effective in an unselected SSc population [38]. Thus, years of focused, collaborative, multinational research have validated the effectiveness of systematic, routine early detection and screening programs for SSc-PAH. This is in contrast to recommendations for other CTDs, where guidelines suggest screening only subsequent to the development of symptoms concerning for PAH [39, 40]. MCTD and CTDs with prominent scleroderma features are considered scleroderma spectrum diseases, and thus guidelines recommend annual screening for PAH associated with these disorders [31].

SLE-PAH

The natural history of PAH associated with systemic lupus erythematosus (SLE-PAH) appears to be different from that of SSc-PAH. For example, studies performed in the Western world indicate that a majority of new SLE-PAH cases may be mild and symptomatic [41], and the prognosis with modern therapies may be significantly better in SLE-PAH compared to SSc-PAH [42]. Another study involving the French Pulmonary Hypertension Registry found the mean time to diagnosis of SLE-PAH is nearly 5 years after diagnosis of SLE, with three-quarters meeting criteria for World Health Organization III or IV functional class [30]. This same study identified anti-SSA and anti-SSB as potential risk factors for SLE-PAH, and the presence of anti-U1-RNP may be a protective factor with regard to survival [30]. Despite these advances in the understanding of SLE-PAH, no early detection algorithm has resulted, nor is the screening of asymptomatic individuals recommended in guidelines [31, 39]. This may be due, in part, to a low pretest probability of SLE-PAH among Western Countries. Between 2004 and 2009, Ruiz-Irastora and colleagues evaluated Spanish patients with SLE for new cases of PAH independent of symptoms and found no new cases of SLE-PAH [43]. Pérez-Peñate and colleagues found similar results in patients with SLE screened prospectively for PAH, in which no new cases of SLE-PAH were discovered through screening [44]. Given the increased prevalence of SLE in Eastern countries compared to Western countries, there is a critical need to evaluate the potential impact of formalized SLE-PAH early detection and screening programs in the Eastern world. The Screening of Pulmonary Hypertension in Systemic Lupus

Erythematosus (SOPHIE) study is an ongoing prospective study applying PAH screening measures, similar to the DETECT study, to patients with SLE in China [13].

Other CTDs

Current data does not support routine programs for the early diagnosis of, or screening of asymptomatic patients for, PAH associated with other CTDs. Nevertheless, PAH may develop in this population and studies suggest that aggressive upfront therapy may improve outcomes [45, 46]. Thus, practitioners must remain vigilant for the earliest signs and symptoms of CTD-PAH and pursue further evaluation on a case-by-case basis.

Treatment of CTD-PAH

Given that it is Group 1 PAH, PAH-specific therapies are all treatment options for patients diagnosed with CTD-PAH, and treatment should follow the same algorithms that are used for idiopathic PAH (IPAH) [39]. Options for Group 1 PAH include endothelin receptor antagonists (ERAs), PDE-5 inhibitors (PDE5is), guanylate cyclase stimulators (sGC), prostacyclin analogues and prostacyclin receptor agonists. While these medications have been shown to be effective in CTD-PAH, the magnitude of the treatment response may be lower than in IPAH [39, 47]. It is also important to note that treatment of CTD-PAH is more complex than treatment of IPAH, as treatment of the underlying CTD often requires the addition of immunosuppressants. These distinctions emphasize the need for close follow-up and multidisciplinary management of patients diagnosed with CTD-PAH. A comprehensive overview of the use of PAH-specific medications in Group 1 PAH is beyond the scope of this chapter, but subgroup analyses of CTD-PAH patients included in trials involving Group 1 PAH have revealed some important insights.

Selexipag

Selexipag is an oral, selective IP prostacyclin agonist, structurally distinct from prostacyclin itself [48]. Subgroup analysis of CTD-PAH patients included in the GRIPHON trial demonstrated that the treatment effect of selexipag on the primary composite endpoint of morbidity and mortality in the CTD-PAH subgroup was consistent with the effect in the overall Group 1 PAH study population [46]. Overall, selexipag reduced the risk of composite morbidity/mortality events of patients with CTD-PAH by 41% [46]. Importantly, this subgroup analysis also

described a more rapid progression of SSc-PAH compared to SLE-PAH in both the selexipag and placebo groups.

Riociguat

Riociguat is a soluble guanylate cyclase stimulator which increases nitric oxide and promotes vascular smooth muscle relaxation. The Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (PATENT-1) was a phase 3, double-blinded, randomized control trial of riociguat which was performed on 443 patients with symptomatic PAH, a pulmonary vascular resistance >300 dyn·sec·cm–5, a mean pulmonary-artery pressure of at least 25 mmHg, and a 6-minute walk distance of 150 to 450 meters. Of these patients, 111 patients carried a diagnosis of PAH-CTD [49]. Patients were randomized to placebo or either high-dose (2.5 mg TID) or lower-dose (1.5 mg TID) riociguat, and the primary endpoint of six-minute walk distance (6MWD) was observed. The study found that 6MWD improved significantly in the treatment group over the treatment time of 12 weeks by a mean of 30 meters in the higher-dose group. As presented in the supplementary appendix, this effect persisted in the connective tissue disease (CTD) subgroup. Of the 96 patients with CTD who completed the trial, the mean change in 6MWD for riociguat was positive 18 meters compared to negative 8 meters observed in the placebo group. Furthermore, PATENT-2, the extension study for this trial, observed that these improvements in functional capacity persisted over the extension period of 1 year [50].

Immunosuppression

There is fairly limited data on immunosuppression's role in PAH-CTD. A 2008 retrospective analysis investigated the role of first-line immunosuppression in PAH. In this analysis of 23 patients treated with or without pulmonary vasodilators at baseline, patients were treated with 6 months of cyclophosphamide then a prednisone burst and taper, followed by maintenance immunosuppression at discretion of rheumatologist. Seventeen patients received immunosuppression alone and six in combination with PAH vasodilator therapy (three with bosentan, three with epoprostenol, and one with treprostinil). This analysis found that 8 of 16 (50%) of SLE- or MCTD-associated PAH patients responded to first-line immunosuppression alone, and 4 of 7 (57.1%) of those treated with both immunosuppression and vasodilators were responders, reporting improved NYHA functional class, 6-minute walking distances, and mean pulmonary artery pressures. Furthermore, responders were more likely to have better baseline functionality and hemodynamic parameters [51].

Conclusion and Future Directions

At present, epidemiologic and clinical trial data support the use of standardized, routine early detection and screening programs for PAH in patients with scleroderma spectrum diseases. Furthermore, early, aggressive treatment has been shown to alter the clinical course of SSc-PAH. A pressing need exists to more fully elucidate the epidemiology of other CTD-PAH subtypes on a global scale. This is especially important in the Asia-Pacific region, where the prevalence of SLE-PAH is much higher than in the Western world. Well-designed epidemiological studies that accurately assess the regional prevalence of both CTD subtypes as well as CTD-PAH (diagnosed by right heart catheterization) have the potential to improve outcomes by identifying regions that may benefit from early detection and screening programs. In addition, it is important to continue the recent trend of using prespecified, subgroup analyses in clinical trials that help to both better characterize CTD subgroups and assess the potential for variations in drug response.

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