

How should we treat vascular and fibrotic lung disease in scleroderma?

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Abstract

Recent randomized trials suggest that evidence-based algorithms for systemic sclerosis can be developed to identify patients at risk for lung disease, follow lung disease progression, and modify disease with therapies of proven benefit. Recognition of disease subsets allows physicians to integrate physiology, overlapping disease manifestations, and predictable drug effects into a comprehensive disease management program.

Introduction and context

Pulmonary disease is the leading cause of morbidity and mortality from systemic sclerosis (SSc) [1]. The two most common pulmonary complications of SSc are interstitial lung disease (SSc-ILD) and pulmonary arterial hypertension (SSc-PAH). Management focuses on declaring all SSc patients at risk for these complications, prompting mandatory screening for lung disease.

SSc-ILD is present in up to 80% of patients when objectively assessed with computed tomography (CT) [2]. Defining who needs treatment remains controversial. Similarly, SSc-PAH may be clinically silent at early stages. Although the estimated prevalence of SSc-PAH is 27% [3], it tends to occur a decade or more following disease onset [4].

The risk of SSc-ILD appears highest in the diffuse cutaneous (dc-SSc) subset of disease, and the risk of SSc-PAH appears highest in the limited cutaneous (lc-SSc) subset. Gene expression studies reveal widespread differences in the basic biological features of these two subsets [5], with some experts considering them completely independent diseases. Recent studies, however, show blurring of the clinical boundaries between the subsets with regard to ILD risk [6].

dc-SSc, particularly if characterized by autoantibodies to DNA topoisomerase-1 (anti-Scl-70) [7], frequently leads to aggressive SSc-ILD. Since the greatest decline in forced vital capacity (FVC) occurs within the first 5 years [8], all patients should receive serial pulmonary function testing. Screening CT remains controversial as many will be abnormal in the absence of pulmonary symptoms or evidence of declining lung function.

lc-SSc, characterized by an anti-centromere autoantibody pattern on anti-nuclear antibody testing, often leads to more severe vascular disease. Raynaud syndrome with digital ulcerations frequently precedes SSc-PAH [4], the most common cause of death in this subset. Diffusion capacity of the lung for carbon monoxide (D_LCO) reduction in isolation [9] and an increased predicted FVC percentage/predicted D_LCO percentage ratio [4] are risk factors. Right heart catheterization remains the gold standard to confirm a PAH diagnosis.

Treatment of SSc-ILD to date has been haphazard, with a variety of therapies applied and reported in case series and randomized trials [10,11]. In the majority of patients, the disease slowly progresses with an estimated mortality of 42% within 10 years [12]. Therefore, treatment trials to prove efficacy must be, by necessity,

of long duration and/or involve large numbers of patients.

The previous 1-year mortality of 50% reported in SSc-PAH [13], on the contrary, is not seen in the current treatment era [14] as treatment options have expanded. A broad consensus that long-term placebo-controlled trials in SSc-PAH are not ethical has emerged, despite the fact that none of the current drug trials has been subjected to the rigors necessary to prove a survival benefit of PAH drugs.

Another conundrum faced by physicians is the SSc patient with both pulmonary hypertension (PH) and SSc-ILD [15]. PH results from vascular destruction by the fibrosis of ILD, pulmonary arteriolar remodeling and plexiform arteriopathy (SSc-PAH), or pulmonary venous hypertension due most commonly to a non-compliant left ventricle (LV) resulting in diastolic dysfunction. Pathologically, myocardial fibrosis without muscular hypertrophy has been noted in SSc autopsy series as a common finding [16].

Recent advances

Interstitial lung disease

In clinical trials, the most robust endpoint for progressive lung function decline in SSc-ILD is FVC; however, the decline may not be linear. In a retrospective review [17], if a baseline predicted FVC of less than 80% occurred by 3 years compared with 5 years after disease onset, a further decline of at least 15% was more likely in the early-onset group.

Another study [18] defined disease extent on CT as mild (<10% involvement) or extensive (>30% involvement) and demonstrated that extensive disease was associated with further FVC and D_LCO decline, and a higher mortality. Combined, these two studies suggest that early ILD onset and more severe disease are more prone to further advance. Biologically, the concept that fibrosis begets more fibrosis implies that the patients likely to benefit from treatment are those with the most extensive disease.

The Scleroderma Lung Study (SLS) [19] and the Fibrosing Alveolitis in Scleroderma Trial (FAST) [20], using oral or intravenous cyclophosphamide (CYC), respectively, showed comparable results of a modest preservation of FVC in the CYC-treated subjects during the time of active treatment. In SLS, secondary outcomes also improved, including Short-Form 36 quality-of-life scores [21]. These studies suggest that SSc-ILD is treatable, but longer-term effective treatment options are needed. Our current treatment practice is an

18-month oral CYC course, with dose determined by toxicity monitoring, followed by a drug holiday. Whether mycophenolate mofetil will be able to replace or extend the CYC treatment effect remains to be determined in clinical trials.

Pulmonary arterial hypertension

SSc-PAH therapy appears to improve survival compared with historical controls [14]. Most clinical trial cohorts, however, include SSc patients as a subgroup of other PAH disease states. These studies conclude that the outcome for SSc-PAH is not as good as for idiopathic PAH [22], although the reason for this observation is unclear. Most experts speculate that the systemic nature of SSc adds vascular morbidity to other organ systems and affects outcome. Furthermore, many SSc patients enrolled in PAH trials are allowed to enter when a mild amount of ILD or LV dysfunction is present.

SSc patients with both clinically significant ILD and PH, however, are excluded from all current studies. Our treatment experience is similar to that of others [23]. This group has high baseline predicted mortality and yet can have a beneficial clinical response when thoughtfully treated for the individual disease components. We begin with a right and left heart catheterization to define the extent of LV disease before beginning therapy for PAH, SSc-ILD, and LV diastolic dysfunction if present. Since the 6-minute walk test is useful for defining improvement in all of these disease states, we use this test to define whether clinical improvement is occurring, provided that the distance walked is dyspnea-limited [24].

Implications for clinical practice

Every SSc patient should be screened with serial spirometry. Abnormal spirometry should prompt a more comprehensive evaluation with CT and echocardiography. Dyspnea in the presence of normal spirometry should also be evaluated with CT and echocardiography, and if these prove normal, more intensive evaluation should be done. Treatment decisions for ILD include a thoughtful evaluation of disease extent and patient preferences, since delays in treatment until the predicted FVC is less than 70% or the CT extent is greater than 30% could be associated with disabling symptoms that may be incompletely reversed. Treatment decisions concerning PAH therapy are currently based on World Health Organization class and are similar to other PAH disease states as recommended by guidelines [25].

Abbreviations

CT, computed tomography; CYC, cyclophosphamide; dc-SSc, diffuse cutaneous systemic sclerosis; D_LCO ,

diffusion capacity of the lung for carbon monoxide; FAST, Fibrosing Alveolitis in Scleroderma Trial; FVC, forced vital capacity; lc-SSc, limited cutaneous systemic sclerosis; LV, left ventricle; PH, pulmonary hypertension; SLS, Scleroderma Lung Study; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-related interstitial lung disease; SSc-PAH, systemic sclerosis-related pulmonary arterial hypertension.

Competing interests

JNK declares that he has no competing interests. CS has been a consultant for Actelion (Allschwil, Switzerland), Encysive (Houston, TX, USA), and Gilead (Foster City, CA, USA). He performs clinical trials with funding from the National Institutes of Health (Bethesda, MD, USA), Actelion, Pfizer Inc (New York, NY, USA), and FibroGen (San Francisco, CA, USA) and is on the speakers' bureau for Actelion and Gilead.

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