Patient and Physician Perspectives on Systemic Sclerosis–Associated Interstitial Lung Disease

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ABSTRACT: Systemic sclerosis–associated interstitial lung disease is challenging to diagnose and treat. Patients and physicians can perceive the disease differently and have different views on its management. Communication issues between them can lead to suboptimal disease management. Despite a clear need for improvement in the speed and accuracy of the diagnostic workup, the heterogeneity of clinical symptoms renders the process long and challenging. When considering treatment options, physicians may be more focused on the evidence supporting a particular treatment or on a patient's pulmonary function test results, as opposed to the realities of the patient's difficulties with symptoms or the psychosocial effects of systemic sclerosis–associated interstitial lung disease. Disease management plans should be determined by the patient's own preferences and goals as well as the objective clinical situation. Health care providers must consider their patients as partners on a journey in which treatment decisions are reached jointly. This review will focus on the perspectives of physicians and patients in relation to the diagnosis and management of systemic sclerosis–associated interstitial lung disease. Similarities and differences in these perspectives will be identified, and strategies for achieving optimal disease management will be proposed.

KEYWORDS: Interstitial lung disease (ILD), patient, perspectives, physician, scleroderma/systemic sclerosis (SSc)

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Introduction

Systemic sclerosis (SSc), also known as scleroderma, is a systemic autoimmune disease that affects the skin and internal organs, particularly the lungs, kidney, heart, and gastrointestinal tract.[1,2] Systemic sclerosis reduces quality of life and causes significant morbidity and mortality. It has a major financial impact, both on the health care system and the patient. Although any organ system can be affected, the leading causes of death in SSc involve the pulmonary system. The 2 most common pulmonary manifestations are pulmonary hypertension and interstitial lung disease (ILD), accounting for ~60% of SSc-associated mortality.[1,3-6] In this review, we will focus on the diagnosis, treatment, and clinician and patient perspectives on ILD.

As a multidisciplinary team of experts in SSc-associated ILD (SSc-ILD), including pulmonologists, rheumatologists, and a patient-advocate, who is also a patient with SSc-ILD, we reviewed the literature describing the diagnosis and treatment of SSc-ILD to evaluate the current disease management approach. Based on our collective experience, we compare our perspectives on SSc-ILD management and suggest strategies for achieving closer alignment of our goals to achieve optimal disease management.

Pathogenesis

The pathogenesis of SSc-ILD is believed to involve persistent and repeated bouts of injury to endothelial cells, activation of the immune response, and fibroblast recruitment and activation that results in fibrosis or scarring.[5] Patients with SSc-ILD usually present with exertional dyspnea, fatigue, nonproductive cough, and bilateral basilar inspiratory crackles on auscultation.[7,8] Systemic sclerosis–associated interstitial lung disease can be asymptomatic in the early stages, and symptoms are likely to emerge as the disease progresses.[9]

The multi-organ systemic nature and heterogeneity in clinical signs of SSc-ILD can make differential diagnosis and disease management a challenge. In addition, patients and physicians can have differing views on the disease and how it should be managed. It can be difficult for patients to develop a clear understanding of the diagnosis, prognosis, and treatment options.[10,11] However, if patients are not educated about the disease and its course, key patient priorities may not be addressed. Communication challenges between patients and physicians can lead to suboptimal disease management. Ideally, clinicians and patients should work together to understand each other's perceptions of SSc-ILD.

This review will focus on our perspectives as a multidisciplinary team, including specialist pulmonologists, rheumatologists, and a patient, in relation to the diagnosis and management of SSc-ILD. Similarities and differences in our perspectives will be identified, and strategies for achieving optimal disease management will be proposed.

Diagnosis

Diagnosis of SSc-ILD is often complicated and delayed by the heterogeneous and nonspecific symptoms associated with both

SSc and ILD, the similarity of SSc-ILD with other ILDs, and the fact that SSc-ILD is a rare condition with which physicians may be unfamiliar. A study involving 1129 patients revealed that the median time to diagnosis of SSc was 2.8 years after onset of Raynaud's phenomenon and 0.9 years after onset of the first non-Raynaud's disease manifestation.[12] This initial diagnosis of SSc is likely to be made by a primary-care physician or a rheumatologist. In patients who develop SSc-ILD, the diagnosis of SSc-ILD may be further delayed due to misdiagnosis and failures in early referral of patients after ILD symptom onset. On average, it can take a patient with SSc up to 7 months to be referred after onset of ILD symptoms.[13] In a survey evaluating the diagnostic experiences of 600 patients with ILD (of whom approximately one-third had an autoimmune disease), nearly all participants initially consulted a primary-care physician; however, only 28% were referred to a specialist after their first visit.[13] For 88% of respondents, the final diagnosis was made by a pulmonologist, with 35% reporting diagnosis by physicians from expert ILD centers.[13]

Systemic sclerosis–associated interstitial lung disease diagnosis may be further complicated as patients with SSc-ILD may initially be asymptomatic and, therefore, may not undergo pulmonary function tests (PFTs) or diagnostic radiology until they present with symptoms such as dyspnea on exertion and a persistent cough. This can be problematic, however, as lung function often declines rapidly within the first 3 to 4 years of the disease. Robust screening procedures and early referral to a pulmonologist are essential to increase the chance of early diagnosis and, hopefully, early treatment. Nevertheless, unlike with other ILDs, because most patients with SSc-ILD are diagnosed with SSc prior to the development of any symptoms related to ILD, the question of other diagnoses is less problematic.

High-resolution computed tomography (HRCT) of the chest is the preferred method for diagnosing SSc-ILD.[7,14,15] On HRCT, SSc-ILD is usually associated with a nonspecific interstitial pneumonia pattern which is characterized by ground-glass opacities usually present on the periphery and the bases of the lungs. Honeycombing and traction bronchiectasis, consistent with usual interstitial pneumonia, may also be seen in later stages of the disease.[7,16] Pulmonary function tests provide useful additional information, enabling the severity of pulmonary symptoms to be evaluated.

We have summarized the key roles of physicians involved in the diagnosis and management of SSc-ILD in Figure 1.

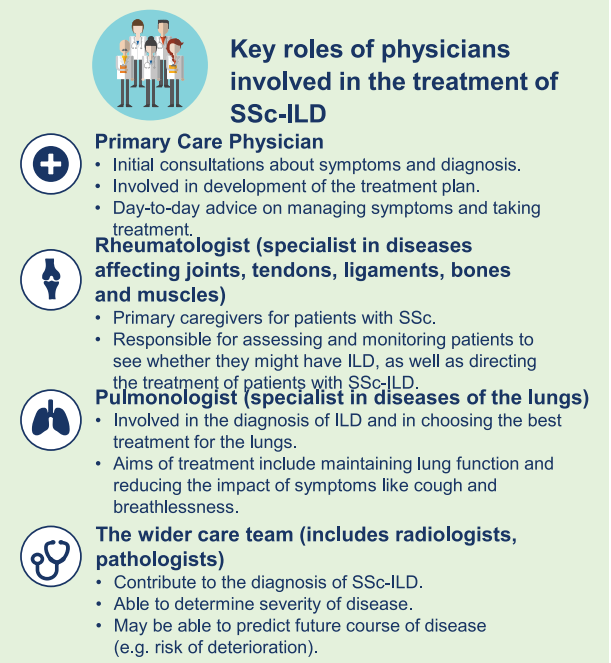

Figure 1. Key roles of physicians involved in the treatment of SSc-ILD. ILD indicates interstitial lung disease; SSc, systemic sclerosis.

Treatment

The antifibrotic agent nintedanib recently became the first Food and Drug Administration (FDA)-approved treatment for SSc-ILD in the United States.[17] It is indicated for slowing the rate of decline in pulmonary function in patients with SSc-ILD based on the results of the phase 3, randomized, double-blind, placebo-controlled Safety and Efficacy of Nintedanib in Systemic Sclerosis trial (NCT02597933).[18] Nonselective immunosuppressing agents, such as cyclophosphamide and mycophenolate mofetil, are recommended for the treatment of SSc-ILD.[7,19-21] Systemic sclerosis–associated interstitial lung disease, however, is often progressive and current treatment strategies are not curative, perpetuating SSc-ILD as a major cause of morbidity and mortality.[5] Novel therapies, including rituximab[22] and hematopoietic stem cell transplantation (suitable only for selected patients and used primarily for cutaneous involvement), have shown some promising results but further research is needed.[7,23] Antifibrotic therapies are continuing to be investigated in SSc-ILD.[24,25]

Lung transplantation is potentially a life-saving option, but it is a major procedure and may not always be feasible due to contraindications, particularly when other organs are involved.[7] Esophageal dysmotility and gastroesophageal reflux disease associated with SSc are major concerns in this regard. Some have expressed concern that extrapulmonary manifestations of SSc may lead to posttransplant mortality; only select centers are willing to carry out lung transplantations in patients with SSc-ILD. In a systematic review evaluating the post-lung transplantation survival of patients with SSc, 7 observational studies (no randomized clinical trials) involving patients with SSc who underwent single lung, double lung, or heart-lung transplantation were identified.[26] The review concluded that the short-term and intermediate-term posttransplantation survival in patients with SSc was similar to those in patients without SSc (ie, idiopathic pulmonary hypertension and non-SSc-ILD) and found no reports of recurrence of SSc in the lung allograft. The findings indicate that concerns regarding posttransplant mortality in patients with SSc-ILD may not

be as important as previously thought.[26] More recently, a single-center retrospective study investigated lung transplantation in SSc, with particular focus on patients with esophageal dysfunction. Outcomes in patients with SSc who underwent lung transplantation were compared with patients with non-SSc conditions or diffuse fibrotic lung disease, or with matched groups (matched groups were composed of lung transplant recipients who did not have SSc, matched to lung transplant recipients with SSc through Greedy distance matching) who underwent lung transplantation, from 2000 to 2012.[27] Patients who received a lung transplant and had, or did not have, SSc were similar in terms of survival, primary graft dysfunction, acute rejection, bronchiolitis obliterans syndrome, and microbiology of respiratory isolates. Esophageal dysfunction was found to rarely preclude active listing for lung transplantation.[27] Nonetheless, the literature is relatively sparse regarding lung transplantation in patients with SSc-ILD, and improved understanding of post-lung transplant comorbidities will likely benefit patient outcomes survival.

In patients with long-standing stable disease or early nonprogressive disease, treatment is not always indicated, and the best option may be supportive care.[28]

Physician perspectives

Currently, physicians monitor SSc-ILD by assessing changes in objective measurements (eg, forced vital capacity percent, extent of fibrosis on HRCT) and subjective assessments (eg, patients' perceptions of their symptoms).[1,7] However, the overall impact of disease on patients' quality of life, personal experiences, and expectations is not well-characterized.

The goal of a health care provider is to improve their patients' symptoms and long-term outcomes. The focus is often on improving quantitative test results rather than the impact of the disease on the patient's personal and social life. The principal concerns of patients with SSc-ILD include psychosocial effects as well as the impact of specific symptoms. It is, therefore, incumbent upon health care providers to understand each patient's concerns and to prioritize them when devising a disease management plan.

Once a patient has been diagnosed, it is important that they are provided with resources to help them understand their illness and the available treatments. Some patients may also be interested in clinical trials and the development of future treatments. The more knowledge a patient can gain, the better prepared they will be to respond appropriately when receiving advice, and to gain a positive outlook.

An international initiative to develop, validate, and improve outcome measurements in rheumatology (OMERACT) was established in 1992, and the organization is active in reviewing the management of rheumatologic conditions, including SSc-ILD.[29] The perspectives of patients with connective tissue disease–related ILD (CTD-ILD) were investigated in an OMERACT study with the aims of identifying areas of unmet need and developing patient-reported outcome measures.[30] Six focus groups were convened, and questions were asked to capture the personal and pathophysiological impacts of CTD-ILD. Subsequently, the study participants completed a questionnaire in which they were asked to ascribe importance to a range of concepts and to describe anything that had been overlooked. In the biophysiological realm, cough and dyspnea were the 2 major themes and patients discussed them repeatedly. Both cough and dyspnea adversely affected physical function, social participation, and activities of daily living. Interestingly, neither "shortness of breath" nor "breathlessness" (commonly used by healthcare professionals) were applied frequently as descriptors for dyspnea; instead, "winded," "trouble getting a breath in," "huffing-puffing," "chest tightening," and others were used. In the psychosocial realm, 2 main themes emerged: living with uncertainty, struggle over self-identity (preserving autonomy and individuality), and self-efficacy (self-management and disease-related relations with family and friends).[30] Communication with health care providers was highlighted as a potential source of uncertainty and anxiety (eg, in relation to how their respiratory disease relates to the CTD, or when to seek urgent medical attention). Delays in obtaining a diagnosis for ILD were another key concern. Many individuals wanted to understand more about their disease and voiced a desire to join a support group, but such groups are not easily accessible to all patients.

The OMERACT study provided a degree of comparison of disease perceptions between physicians and patients, as patients were asked to provide their views on questionnaire concepts suggested by pulmonologists and rheumatologists.[30] Patients considered all proposed questionnaire items to be important (ranging from moderately to extremely important) and did not introduce any new items. This suggests considerable overlap between the perceptions of physicians and patients. However, the physicians had been selected on the basis of their expertise in ILD; it is possible that there would have been a lower extent of overlap in perceptions between the 2 groups, had the physicians been selected randomly.

Some degree of difference between the 2 groups is inevitable as opinions naturally vary between individuals. Efforts are, therefore, needed to maximize the extent of overlap and to ensure that latent differences are understood by both patients and physicians.

From a rheumatologist's perspective (V.D.S.). Rheumatologists are usually the primary caregivers for patients with SSc and are responsible for conducting full assessments for ILD at the time of diagnosis, as well as regularly monitoring patients, particularly those who have greater risk of developing ILD.[31] Common initial symptoms in SSc include Raynaud's phenomenon, swollen fingers, and skin thickening, while dyspnea and cough may also occur as early symptoms in SSc-ILD.[31-33]

In addition to HRCT scans and PFTs, all patients with SSc should undergo an echocardiogram at the time of diagnosis because cardiopulmonary disease and pulmonary arterial hypertension secondary to ILD (ie, World Health Organization group III) are major causes of morbidity.[31] Risk factors for ILD in patients with SSc include African American ethnicity, male sex, diffuse cutaneous SSc, presence of anti-Scl 70 (anti-topoisomerase) antibodies or antinuclear antibodies with a nucleolar pattern, and the absence of anticentromere antibodies.[9,34,35] Abnormal PFTs may help confirm the presence of SSc-ILD, although pulmonary function can be normal during the early stages of the disease and not all lung restriction is caused by ILD.[14,33,36,37] It is recommended that all patients with suspected SSc-ILD undergo HRCT to confirm the diagnosis and to evaluate the extent of ILD.[14,31,37] More than 80% of patients with SSc have some extent of ILD, but not all require treatment. Lung involvement exceeding 20% on HRCT, as described in the staging system proposed by Goh et al,[38] is a key predictor of outcome.[38] Pulmonary function tests should be performed regularly, for example, every 4 to 6 months, to determine the rate of progression.[7] Cut-off values for interpreting normal spirometry can be difficult to define; therefore, regular follow-up to detect changes in lung function is critical even in the absence of symptoms or worsening of symptoms.

Patients in whom interstitial lung abnormalities (ILAs) are observed on computed tomography, despite not having a history of ILD, have higher risk of all-cause mortality than patients without ILAs.[39] Therefore, although 20% of lung involvement is considered an important predictor of outcome,[38] the presence of ILAs should also be considered carefully, especially in those who may be at higher risk of developing ILD such as patients with SSc. A recent study in patients with SSc showed that the presence of lung fibrosis, regardless of extent, was associated with increased mortality.[40] Both studies highlight the importance and need for rigorous screening for ILAs and ILD in patients with SSc, to facilitate early diagnosis and inform early treatment of SSc-ILD.

Early medical intervention can reduce the rate of disease progression; therefore, it is important to explain the necessity of early medical intervention to patients who often may have minimal respiratory symptoms at that time. When faced with a patient with SSc-ILD, it is important to ascertain the risk of progression to decide whether and how intensively to treat the condition. Patients can be classified based on the stage, activity, and severity of disease.[9,38] It is advisable for all patients with SSc-ILD to receive preventive treatment for gastroesophageal reflux (helping to prevent microaspiration) and immunization against pneumonia and influenza.[33,41] Patients should also be encouraged to undertake exercise programs, which can help with pulmonary rehabilitation.[42] Regular evaluation should be performed to ensure that hypoxemia is detected quickly.

From a pulmonologist's perspective (T.J.C., M.Y., and A.N.B.). Patients usually present to pulmonologists with dyspnea upon exertion, and this may be the first manifestation of SSc-ILD.[33] Raynaud's phenomenon and skin thickening usually appear before pulmonary symptoms, although they may be subtle and only manifested by cold intolerance and puffy fingers. Cough is a frequent symptom of significant importance to patients with SSc-ILD, but it is not always prioritized by clinicians as a key assessment parameter.[43,44] The diagnosis of SSc-ILD can be difficult because symptoms and features of the disease are similar to other ILDs; it is critical, therefore, for the pulmonologist to evaluate all clinical signs, symptoms, and laboratory test results (including tests for antinuclear and anti-Scl 70 antibodies),[8,45,46] and to consider the potential impact of connective tissue disease. Immunosuppressive drugs, such as cyclophosphamide or mycophenolate mofetil, are the mainstay of treatment for SSc-ILD.[47] Further treatments such as rituximab, abatacept, and the antifibrotic drug pirfenidone are also being investigated.[7,47] Corticosteroids are sometimes administered in combination with immunosuppressants, but doses should be kept low to avoid the risk of renal crisis.[47] Supportive therapy (eg, cough suppression, oxygen support, pulmonary rehabilitation) should also be adopted as appropriate. For patients with acute exacerbations of SSc-ILD, there is a tendency to use high-dose corticosteroids, but the evidence supporting this approach is weak[48] and high-dose steroids are not recommended in this setting.

On average, patients are diagnosed 7 months after the onset of ILD symptoms and misdiagnoses are common.[13] Limited availability of resources for educating patients on SSc-ILD[49] may contribute to the delay in reaching a diagnosis, as patients may not recognize their symptoms as manifestations of ILD and, therefore, may not report them to their health care provider. There is a clear need to improve the speed and accuracy of ILD diagnosis, and improved patient education may help to address this need. Further potential measures include education of health care professionals and the development and implementation of improved diagnostic processes. Pulmonologists are particularly important once the diagnosis of ILD has been established. As mentioned, cough is very common and is often considered by patients to be one of the most bothersome symptoms.[50] However, there are many possible causes of cough (eg, gastroesophageal reflux, bronchospasm, allergy, nasal drainage, and ILD). The pulmonologist is required to establish the determining factor(s) and the appropriate treatment. It is important to determine the presence of hypoxemia during exercise, and the use of a forehead probe when doing the 6-minute walk test is necessary because patients with SSc with Raynaud's phenomenon have fingers that register oxygen saturation inaccurately during exercise. When hypoxemia is present, it is vital to prescribe oxygen therapy and to educate the patient about the importance of this treatment both for improving symptoms and for preventing the development of secondary pulmonary

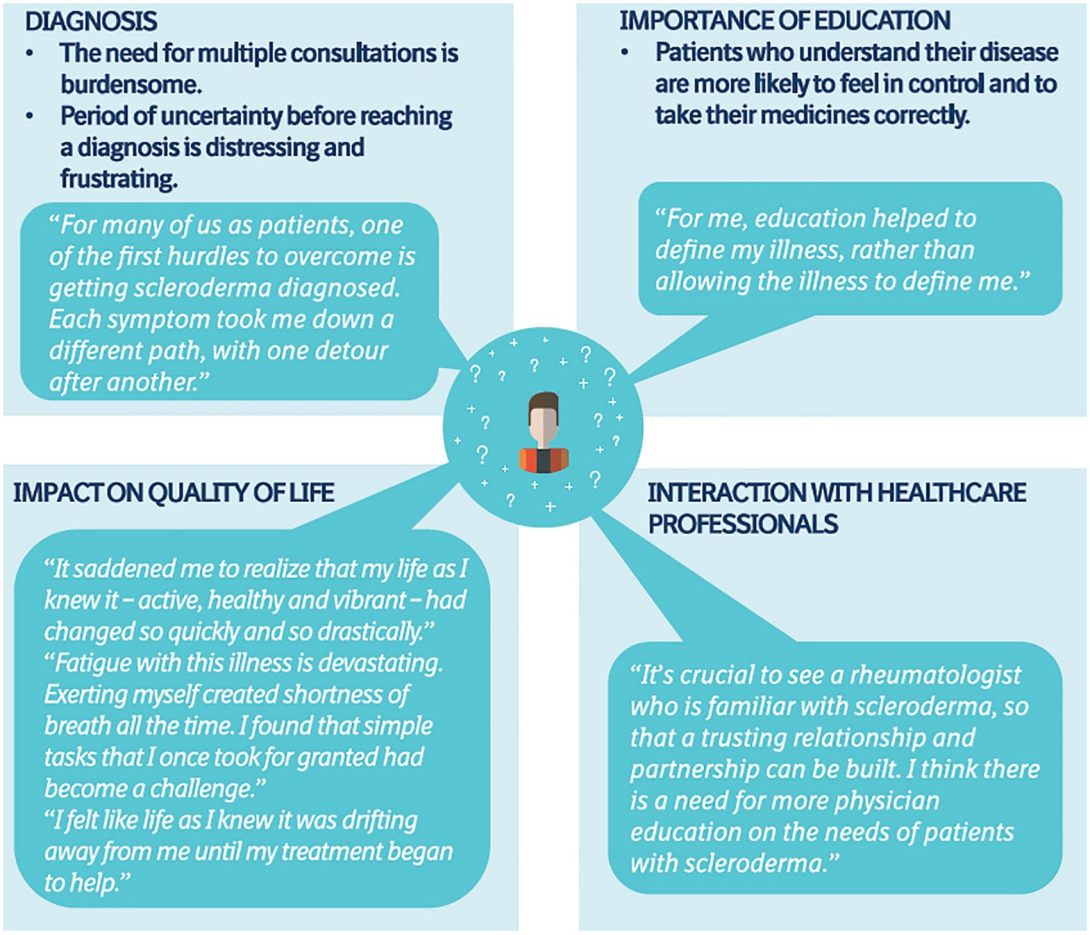

Figure 2. A patient's key concerns regarding the management of SSc-ILD. ILD indicates interstitial lung disease; SSc, systemic sclerosis.

hypertension. Pulmonary rehabilitation may also be helpful for patients with hypoxemia.[42]

The wider care team (collective perspective of all authors). In clinical practice, the use of a multidisciplinary team is beneficial in all ILDs and is currently considered the "gold standard" for reaching a definitive diagnosis and determining management.[51] Multidisciplinary meetings usually involve pulmonologists, rheumatologists, thoracic radiologists, and thoracic pathologists,[52] but can also include patients, their families, nurses, and other subspecialists involved in their care. Clear communication during these meetings is key, especially given that patients can have misconceptions about their disease.[49]

The need to improve health care professionals' communications with patients and to involve them in decision-making is increasingly being recognized.[10,11,53] Currently, there are no curative therapies for SSc-ILD and it is important that patients understand this. Nevertheless, as mentioned earlier, there is evidence to support the use of the recently FDA-approved agent nintedanib,[17] and the recommended immunosuppressants, cyclophosphamide, and mycophenolate mofetil.[7,19-21,47] Patients and their families need time to process the diagnosis and treatment plan, and they must be given ample opportunity to ask questions.[10,11] A typical 15-minute clinic appointment is not enough time to discuss how best to manage such a complex disease and minimize its effects on the patient's mental and social well-being. Longer appointment times (eg, 45 minutes) would be challenging to accommodate within current health care systems but could be considered an aspirational target. In all cases, the establishment of a trusting and positive relationship with the patient and their family is important to help them through the difficult journey that SSc-ILD presents.

The patient's care team often goes beyond the physician and may include physician assistants, nurse practitioners, or trainee physicians. These individuals may contribute by recording the patient's history, performing physical examinations, or serving as the patient's first contact by telephone or email.

The roles of rheumatologists, pulmonologists, and the wider care team involved in the care of patients with SSc-ILD regarding treatment, as mentioned above, have been summarized in Figure 1.

From a patient's perspective (N.B.). Systemic sclerosis–associated interstitial lung disease is a heterogeneous disease that affects individuals differently, meaning the extent to which quality of life is impaired varies from patient to patient.[3] Some patients have described living with the disease as bothersome, whereas others find it impossible to live with.

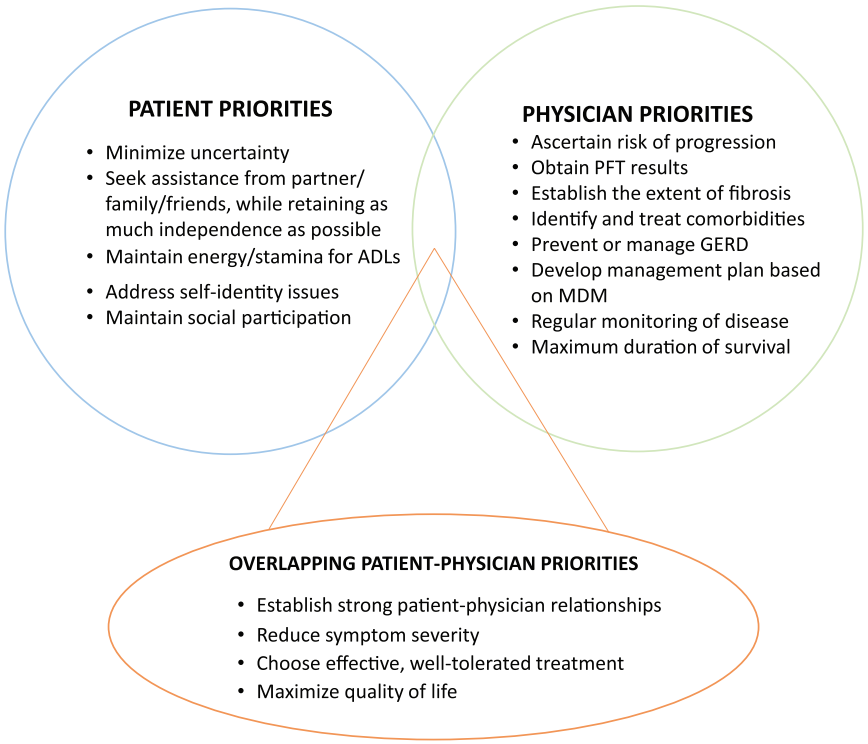

Figure 3. Key priorities of patients and physicians in the management of SSc-ILD. Key priorities of patients are shown in the left circle, key priorities of physician are shown in the right circle, and overlapping priorities are represented in the lower oval. ADLs indicate activities for daily living; GERD, gastroesophageal reflux disease; ILD, interstitial lung disease; MDM, multidisciplinary management; PFT, pulmonary function tests; SSc, systemic sclerosis.

Due to the complexity of SSc-ILD and limited availability of appropriate educational materials, patients often lack detailed understanding of their disease.[49] Misconceptions regarding the cause of SSc-ILD are common, and patients can develop personal views of having developed the disease through vaccination, emotional or psychological shock, pregnancy, or spirituality. Such patients may believe, wrongly, that a change in their lifestyle could reduce disease progression and reverse the disease.[3,49] Moreover, poor understanding of the disease is likely to reduce patients' adherence to prescribed treatment; patients who do not understand their disease may be less likely to perceive the need to take their medication.[54] These are important reasons for helping patients to understand their condition and the available treatments. Knowledge is power; it gives the patient more confidence and helps them feel more in control of their illness. As a patient-advocate for SSc-ILD and a patient with SSc-ILD, I found that education is key; in my own experience, education helped me to define my illness, rather than allowing the illness to define me. A way for patients to gain accurate information and expand their understanding of their disease is through scleroderma patient–focused support groups or associations. Several exist worldwide; we recommend the Scleroderma Foundation (www.scleroderma.org) as a primary resource in the United States for patients and their families.

Regarding the manifestations of SSc-ILD, some patients have described their inability to breathe as, "It's like I'm drowning on land." Figure 2 describes some of my experiences of being diagnosed with SSc-ILD and its impact on my quality of life. In addition, I reiterate my perspective on the importance of education and the importance of effective patient-health care professional interaction.

In my experience as a patient-advocate in SSc-ILD, I have found that my perspectives are common among patients with SSc-ILD. Furthermore, most patients are concerned about not having the physical energy and stamina to complete errands or simple tasks. They also worry about their life expectancy and progressive disability, creating difficulties in life planning.[30] Patients describe using various coping strategies to manage their disease. These include reorganization of physical space, use of aids, pacing of activities to preserve energy while lessening the need/duration for "recovery" and avoidance of cough triggers. They may also try to strike a balance between receiving family support and avoiding negative effects such as perceived overreliance and concerns about changes in family dynamics.[30,49]

Conclusions

Systemic sclerosis–associated interstitial lung disease is a complex, heterogeneous disease that affects individuals differently and is often poorly understood. Per our consolidated perspectives, we have presented key common and contrasting priorities of patients and physicians concerning the management of SSc-ILD in Figure 3. It is important for patients and health care

providers to be aware of potential differences between their perceptions of SSc-ILD. Early and accurate diagnosis of SSc-ILD is important for reducing patients' uncertainty and optimizing prognosis by ensuring opportunities for early treatment are not missed. Disease management plans should be determined by the patient's own preferences and goals, as well as the objective clinical scenario. A multidisciplinary approach is typically needed for efficient diagnosis and treatment of SSc-ILD, which could be facilitated by developing ILD centers. Health care providers should consider their patients as partners on a journey where treatment decisions are reached jointly. As physicians, we are often more focused on the evidence supporting a particular treatment or PFT results than on the patient's difficulties with fatigue, cough, or relationships with others. It is essential that the SSc-ILD care team works together in focusing their efforts on the needs of each individual patient.

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Author Contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). Only the named authors of this manuscript contributed to the content and writing of this manuscript. TJC, MY, ER, ANB, VDS, and NB jointly developed the introduction and results of this article. TJC, MY, ER, and ANB contributed to the sections discussing the pulmonologist and wider care team's perspectives. VDS developed the rheumatologist's perspectives and NB supported the development of the patient's perspectives. All authors contributed to the development of the figures. None of the authors received financial compensation from an external source in return for writing or publishing this paper. All authors have contributed in the preparation of this manuscript.

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