Assessing disease activity in scleroderma-related interstitial lung disease: a review and practical guide to management

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Abstract

Systemic sclerosis (SSc) is a heterogeneous disease with a propensity to involve multiple organ systems. There is a significant proportion of these patients with interstitial lung disease (ILD) who are at risk of mortality and morbidity. There are limited available tools to assess the severity of parenchymal lung involvement, and they are subject to confounding factors, including the presence of pulmonary hypertension and concomitant smoking history. The diagnostic tools include careful clinical history, examination, thoracic imaging, and pulmonary function test. One of the limitations of assessing disease severity in SSc-ILD is the lack of standardized definitions for disease activity and serum biomarkers to predict future progression.

Although there has been significant progress in managing SSc-related ILD over the last couple of decades, with a few randomized double-blind clinical trials assessing the role of immunosuppression (mainly cyclophosphamide and mycophenolate mofetil), the efficacy of these therapies is at best modest and is associated with significant toxicities. Furthermore, nintedanib has shown promise in reducing forced vital capacity decline in SSc-ILD and in progressive fibrotic-ILD of a range of etiologies. Data are emerging for therapies like rituximab and tocilizumab, and we are likely to see further evidence of similar drugs being efficacious in this disease cohort. A relatively simplified algorithm is proposed in this review to guide clinicians dealing with ILD and SSc. It is imperative that clinicians take a multidisciplinary approach to managing this complex disease in a changing therapeutic landscape.

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Introduction

Systemic sclerosis (SSc) is a rare inflammatory disease of unknown origin. It is characterized by vascular dysfunction and progressive fibrosis of the skin with multi-organ involvement. One of the major complications that drives the mortality of SSc patients is interstitial lung disease (ILD). There are two common subtypes of SSc, namely limited cutaneous and diffuse cutaneous. The course of SSc-associated ILD (SSc-ILD) progression has a wide spectrum, ranging from slowly evolving disease to rapid flare-up and deterioration. In most cases, it is diagnosed while evaluating a patient already suspected to have SSc. Occasionally, however, it can be the presenting feature. Since the treatment is based on aggressive immunosuppression, it is important that these therapies are carefully considered in patients with stable and non-progressive disease. The problem, as in other ILDs, is to identify patients at high risk of progression; to select them for early therapeutic interventions. This review aims to provide an update on the diagnosis, assessment of disease activity, and management of patients with SSc-ILD.

Epidemiology

Around 35-50% of patients with SSc develop ILD [1]. Along with pulmonary hypertension and cardiac disease, it represents one of the most significant causes of mortality [2]. The risk of developing SSc-ILD is greatest early in the disease course, especially during the first 3 years [3]. The risk factors for the devel-

opment and progression of SSc-ILD include African ancestry, older age at onset, diffuse cutaneous subtype, shorter disease duration, the presence of anti-topoisomerase I antibodies, and the absence of centromere antibodies [3]. None of these risk factors is absolute; however, it is well recognized that patients with the limited cutaneous form of the disease can also develop ILD [4].

Screening of systemic sclerosis patients for interstitial lung disease

As there is a high proportion of patients with SSc who develop ILD in their disease course, they should be screened for this organ complication at the earliest opportunity. A Delphi study published recently by a Japanese group recommended screening in patients with persistent respiratory symptoms such as shortness of breath, dry cough, or palpitations on exertion [5]. The authors recommend chest auscultation, chest radiograph, and high-resolution computed tomography (HRCT) as screening tools for ILD and suggest considering measurement of KL-6 as a blood screening tool. British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines in 2016 recommended screening all patients with SSc for lung fibrosis, as up to 80% of patients with SSc develop ILD [6]. As there is a paucity of published guidance on this aspect of SSc management, we welcome the anticipated guidelines by BSR on important issues, including screening, monitoring, and management of systemic autoimmune rheumatic diseases (SARDs) [7]. Furthermore, full guidelines from the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) are also expected to be published in the near future. However, the ACR guideline summary recommends screening patients with SARDs having an increased risk of developing ILD, by HRCT and pulmonary function tests (PFTs) as a conditional recommendation [8]. A close collaboration with rheumatologists and pulmonologists trained in the assessment and management of SARDs is critical to identifying SSc-ILD early in the disease course with available screening tools.

Diagnosis of systemic sclerosis-interstitial lung disease

The most widely used classification criteria for scleroderma are the 2013 ACR/EULAR classification criteria [9]. They are primarily designed to facilitate inclusion of these patients into SSc clinical trials, with a score of >9 indicating that a patient can be classified as definite SSc. It is possible for ILD to be the initial manifestation of the disease in SSc and be more severe than other manifestations. In these cases, therapy for ILD may need to be instituted before the patients have entirely fulfilled the classification criteria. It is for this reason that the European League against Rheumatism Scleroderma Trial and Research Group (EUSTAR) has proposed new criteria for very early diagnosis of SSc. This emphasizes the presence of three red flag symptoms (Raynaud's phenomenon, puffy fingers, and antinuclear antibody positivity) plus disease-specific biomarkers (anticentromere antibody, anti-topoisomerase I antibodies) or microvascular alterations detected by nailfold videocapillaroscopy. The presence of these signs should trigger further investigations – in particular, esophageal manometry, HRCT scan, and PFTs [10].

Imaging

HRCT is the "gold standard" non-invasive radiological method for the diagnosis of SSc-ILD and can detect subtle abnormalities at an early stage. The most common pattern seen in SSc-ILD patients is non-specific interstitial pneumonia (NSIP), with a greater proportion of ground-glass opacities (GGOs) and a lower degree of coarse reticulation, predominant in lower lobes with subpleural sparing [11,12]. However, a usual interstitial pneumonia (UIP) pattern can also be seen [11,12]. Honeycomb cysts are seen in up to a third of patients with SSc-ILD and are more common in patients with limited cutaneous SSc. Another radiological sign reported for SSc-ILD is the four-corner sign, with the presence of ground glass change, reticulation, and/or honeycombing in the four corners of the lungs. This has been deemed specific for SSc-ILD [13]. Champtiaux *et al*. reported scleroderma with combined pulmonary fibrosis and emphysema (CPFE) syndrome [14]. They demonstrated that patients with this syndrome were more likely to be male, smokers, and have limited cutaneous variety. Moreover, it was associated with a high incidence of developing pre-capillary pulmonary hypertension. Furthermore, a study carried out by Bonifazi *et al*. evaluated the prevalence of pleuroparenchymal fibroelastosis (PPFE) in patients with SSc from two different referral centers (UK and Italy) and reported a prevalence of PPFE of 18% in the combined population [15]. The presence of PPFE was significantly linked to bronchial abnormalities and worse survival, independent of the severity of ILD or short-term pulmonary function changes.

The patterns seen on HRCT when reported by an experienced radiologist with high confidence can predict the underlying histopathology, with reticulation representing underlying fibrosis on biopsy and ground glass opacities representing inflammation. The picture is complicated, however, because while ground glass opacities usually reflect alveolitis, when there is associated traction bronchiectasis, it can be due to fine fibrosis [16]. Likewise, inflammation can co-exist in areas of honeycombing and reticulation as these may be sites of inflammation within established disease. Reversibility of HRCT changes (with reticular abnormalities) is rare. Instead, the radiological progression seems to be one of the replacements of GGOs with honeycombing, traction bronchiectasis, and/or bronchiolectasis over time [17]. Up to two-thirds of patients with GGOs progress to fibrosis, regardless of therapy [18].

It is important to acknowledge that the accuracy of HRCT scan pattern in relation to histopathological pattern is dependent on the pre-test probability of UIP pattern on HRCT being highly predictive of a UIP pattern on histopathology. However, the diagnostic accuracy in cases of NSIP pattern on computed tomography (CT) scan is not as high as UIP, and patients may turn out to have a UIP pattern on biopsy when the radiological pattern was NSIP or indeterminate for UIP. The expertise of a reporting radiologist is important, as the diagnostic accuracy can be dependent on the experience of the radiologist as part of a multidisciplinary team involved in the diagnostic evaluation. However, inter-observer agreement for UIP pattern amongst thoracic radiologists is moderate as reported by Walsh *et al*., evaluating American Thoracic Society/European Respiratory Society Criteria for UIP among 112 observers [19]. There are some features on HRCT that can provide prognostic value in connective tissue disease-related fibrotic lung disease (CTD-FLD), as reported by a study evaluating 168 patients with CTD-FLD, where HRCT scans were scored by two observers for a variety of patterns. The severity of traction bronchiectasis and extent of honeycombing were associated with mortality in CTD-

FLD, and interobserver agreement was higher for traction bronchiectasis than honeycombing [20]. Hence, although HRCT scan is the best available imaging modality to assess CTD-ILD, the radiological pattern of ILD informing severity, histopathology, and prognosis is dependent on multiple factors, so HRCT imaging should be interpreted in the context of clinical and physiological picture (and co-morbid conditions) along with expertise of a radiologist within the multi-disciplinary team.

Histopathology

The most common histological pattern, NSIP, is characterized by a homogeneous, diffuse involvement of the alveolar interstitium by variable degrees of chronic lymphoplasmacytic infiltrates and fibrosis [11]. The fibrotic variant of NSIP is more common than cellular NSIP, which is characterized by inflammatory infiltrates [21]. The fibrotic variant also carries a worse prognosis. UIP is the second most common interstitial pattern, characterized by a patchwork of temporally heterogeneous fibrosis, including collagen deposition with honeycomb changes and evidence of fibroblastic foci, which are activated myofibroblasts. The UIP pattern confers a worse prognosis as compared to NSIP. Other histopathological patterns have been reported in SSc, including PPFE, pulmonary vascular changes consistent with pulmonary hypertension, aspiration of gastric contents or foreign bodies (due to esophageal dysmotility), peri-bronchial fibrosis, organizing pneumonia, or diffuse alveolar damage [22]. It is important to interpret histopathological findings within the clinical context of the patient, and we are witnessing a decline in surgical lung biopsies in SSc-ILD, as HRCT scans are becoming more informative (due to better resolution), obviating the need for invasive surgical procedures.

Assessment of disease activity

Disease activity in SSc refers to the component of disease severity consisting of reversible inflammation or edema. This contrasts with the concept of assessing disease severity or damage, both of which incorporate irreversible aspects of the disease. Differentiating activity from chronicity or damage is one of the key aspects in the treatment of all rheumatological disorders and dictates the aggressiveness of treatment strategies employed. The relevance of defining some disease manifestations as damage is to clarify, for a clinician, a point of 'no return' in the natural history of a disease or its clinical manifestations, where giving additional immunosuppressive therapy is unlikely to be of benefit. HRCT and PFTs are the most widely used objective markers of active ILD in SSc. However, their application in clinical practice is challenging. The most important markers to monitor are the forced vital capacity (FVC) and the diffusing capacity of lungs for carbon monoxide (DLco), with the percentage change from baseline being critical. A change in the FVC of ≥10% and a change in the DLco of ≥15% are considered significant [23]. Percent predicted DLco is potentially an important marker for the extent of parenchymal disease on CT scan [24]. However, one needs to consider the relative contribution of pulmonary arterial hypertension. Some authors have proposed measuring the FVC: DLco ratio, with a value >1.6 suggesting a greater relative contribution of pulmonary hypertension [25]. Another approach that has been advocated is using the radiographic extent of disease, combined with the FVC to define prognostic subsets – an extent of >20% on HRCT in combination with an FVC <70% indicates extensive disease, and results in poor survival [26]. It is considered more likely that patients with HRCT extent >20% and/or FVC <70% at disease onset will benefit from intensive immunosuppression. This is supported by data from the scleroderma lung study, in which patients with an HRCT extent >50% had an improvement in FVC of 9.81% with cyclophosphamide at 18 months compared to the placebo ($p<0.001$) [27]. Moreover, HRCT provides morphological rather than functional information and is therefore only indirectly related to the disease activity. The determination of inflammatory lung disease on HRCT relies upon the identification of GGOs. The use of positron emission tomography combined with CT (PET-CT) to identify inflammatory GGO in early SSc-ILD has shown some promise. Peelen *et al*. demonstrated that semi-quantitative assessment of ^{18}F-Fluorodeoxyglucose PET-CT is able to distinguish ILD from non-affected lung tissue in SSc [28]. It is important to note that accurate attribution of the etiology of deteriorating spirometry values is not always straightforward. For example, a low FVC, besides being due to ILD, may also be secondary to respiratory muscle weakness or tightening of skin over the chest wall, causing extra-parenchymal restriction, and should be considered before attributing a low FVC to ILD alone. In addition, even in those with confirmed ILD, an active alveolitis may not be the only factor to consider: aspiration of either ingested food and/or gastric contents due to esophageal dysfunction and gastroesophageal reflux is a pervasive feature of SSc, and this is likely to be a contributory factor in ILD pathogenesis and progression in at least a subset of patients [29].

It is imperative for clinicians treating patients with SSc-ILD to be able to appreciate the clinical features that would indicate global disease activity. A perspective that the overall disease is worsening when the state of the lungs themselves is equivocal can bring clarity in treatment decisions. Defining global disease activity in SSc is challenging for several reasons. Firstly, it cannot reliably be done using a single clinical variable. Secondly, patients can present with an indolent course, irrespective of whether or not they belong to either of the two disease subsets, that is, diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc; thirdly, SSc flares can be difficult to be separated from quiescent disease; fourth, the two main morphological manifestations of the disease (interstitial fibrosis and vascular occlusion) may reflect both activity and damage and, finally, validated biological markers reflecting disease activity and behavior are currently lacking.

CPFE can have a major confounding effect on lung physiology in SSc. Hence, we need to recognize that lung physiological parameters may have an impairment secondary to a combination of factors, including CPFE, pulmonary hypertension, and pulmonary vasculopathy without pulmonary hypertension due to large pulmonary vascular reserve. Indeed, Antoniou *et al*. investigated the prevalence of emphysema in a cohort of 333 patients with SSc-ILD and reported an overall prevalence of 12.3% and 7.5% of patients with CPFE were lifelong non-smokers [30]. As expected, a higher proportion of smokers had emphysema (19.7%). These data highlight the complexity of assessment of pulmonary function parameters in SSc-ILD and propose a comprehensive evaluation of these patients, including thorough investigations for pulmonary hypertension, right heart dysfunction, and associated emphysema.

The role of bronchoalveolar lavage (BAL) in assessing disease activity of SSc-ILD has been debated for over two decades, with numerous studies assessing the value of this technique in SSc-ILD. However, the exact value of BAL is still debatable, with more prospective data required before BAL can be recommended

as part of the standard investigatory armory when confronted with SSc-ILD. A recent systematic review by Orlandi *et al*. evaluated 18 studies and noted a positive correlation between BAL neutrophilia and lower FVC as well as DLco [31]. Moreover, there was a lack of consensus for BAL cellularity as a predictor of mortality in ILD associated with SSc. Fractional BAL (FBAL) is a technique that analyzes sequentially collected BAL aliquots independently. Kase *et al*. evaluated FBAL in a retrospective cohort study of 68 patients from a single center in Japan. They reported a significant association between neutrophilia in FBAL-3 (and not pooled BAL) and end-stage SSc-ILD [32]. However, these findings would require confirmation in a prospective, larger multicenter study before FBAL can be recommended as standard investigation in SSc-ILD.

There are a few options for clinicians trying to objectively define the level of disease activity of patients with SSc and including tracking the progression of disease with skin tightness, measuring disease activity cross-sectionally with multiple variables, and longitudinally tracking disease severity over time with a range of variables. The following measurements/indices have been developed to objectively measure disease activity in SSc, and we discuss them briefly in the following section.

European Alliance of Associations for Rheumatology (EULAR) Scleroderma Composite Index

The most recent attempt at deriving a composite disease activity index for SSc was carried out by EUSTAR [33]. After a process of external validation, certain criteria were defined, including the extent of skin involvement, digital ulcers, tendon friction rubs, C-reactive protein (CRP)>1mg/dL, and DLco<70%. They were accorded various weightings, with a score of >2.5 indicating active disease. Low complement levels and the presence of inflammatory arthritis are also valid factors to consider, as they can indicate active disease in patients with overlap syndromes. A high disease activity in early disease, as measured by the European Scleroderma Group Activity Index, has been demonstrated to be a significant predictor of progression and severe organ involvement in dcSSc [33].

Medsger Severity Scale

This scale is based on measuring the severity of disease with scoring that ranges from 0 (normal) to 4 (end-stage) for each organ system involved in scleroderma, including a general measure, along with measures of the peripheral vascular system, skin, joints and tendons, gastrointestinal tract, lung, heart, and kidneys. It has the potential to measure activity if used in the context of serial observations, with worsening severity over time being a surrogate for active disease [34].

Modified Rodnan Skin Score

Modified Rodnan Skin Score (mRSS) is a semi-quantitative measure of skin thickness with a score given from 0-3 at 17 different cutaneous sites. It has been used as a surrogate measure of disease severity and a predictor of the extent of organ involvement and overall prognosis [35]. It is also used as a quantifiable, easily obtainable, and valid score, changing over time in response to therapy. Thus, mRSS is widely used as a measure of disease activity and is employed in clinical trials as a valid primary outcome measure. In patients with diffuse skin disease, improvement in skin score is associated with better clinical outcomes [35]. Furthermore, it is feasible to be used in routine clinical practice, making it an attractive tool for regular use.

Biomarkers for disease severity and progression

There are a number of serological biomarkers to indicate severity and the risk of disease progression. RNA polymerase III antibodies portend an increased risk of renal crisis and malignancy [36]. Patients with serum CRP levels >8 mg/L have more frequent SSc-ILD with worse pulmonary functional impairment (total lung capacity, FVC, DLco) and higher mortality than those with CRP<8 mg/L [37]. In addition, CRP is also associated with worse multi-organ impairment (pulmonary vascular dysfunction, renal, and skin, *etc*.) and is therefore not lung specific. Interestingly, high baseline serum CRP level is also predictive of poor therapeutic response in a small retrospective study, and higher serum levels of IL-6 were also associated with SSc-ILD, with serum levels >7.67 pg/mL linked with increased mortality [hazard ratio (HR)=2.58] at 30 months and a worse lung function impairment [38]. Absolute monocyte count (AMC) at baseline may predict lung function decline as reported recently by Bernstein *et al*. in a post-hoc analysis of the focuSSed trial evaluating tocilizumab in SSc-ILD [39]. There was a significant inverse association between baseline AMC and change in FVC from the baseline to week 48 in the placebo group, but not in the tocilizumab group. The findings propose AMC to be a potential predictor of disease progression in SSc-ILD, especially in those with early disease and elevated serum inflammatory markers.

We are yet to have an ideal single biomarker that is readily available in routine clinical practice with a prognostic value and aid in management decisions during longitudinal follow-up of patients. We may never be able to discover a single biomarker to inform us of risk of progression in SSc-ILD with high accuracy and, likely, a combination of variables including FVC, gas exchange (DLco) and quantitative HRCT scan are the best available parameters to classify disease severity, risk of ILD progression and progression over time as supported by 54 worldwide experts agreeing to a consensus *via* conceptual framework of 80 patient profiles [40]. Furthermore, a decline in FVC of ≥10% from baseline, or a decline in FVC of 5-9% along with a decline in DLco of ≥15% represents progression and can serve as a biomarker for ILD deterioration [41]. Combination of HRCT and PFTs to stage SSc-ILD into limited and extensive disease as per criteria proposed by Goh *et al*. can provide discriminatory information about prognosis and it has been subsequently evaluated by another group of researchers demonstrating good diagnostic performance for radiological extent and prognostic relevance with extensive disease linked with higher risk of death (HR=3.92, 95% confidence interval: 2.12-5.52) [42,43]. Hence, the radio-physiological combination serves as the best available biomarker for SSc-ILD at this stage and should be utilized for this purpose in an appropriate clinical setting.

The role of a multidisciplinary team

Considering the multisystem nature of scleroderma, a multidisciplinary team plays a crucial role; this is not just confined to the diagnosis but should be utilized throughout the management of patients. For SSc-ILD, a panel comprising of rheumatologist, a pulmonologist, a thoracic radiologist, a cardiologist with an interest in vascular disease/pulmonary hypertension, ILD, and rheumatology nurse specialists, and a respiratory occupational/ physiotherapist

should be considered. Taking into account the unpredictable course of the disease helps in developing a robust management plan to help the patient adapt to his symptoms. If there is progression of the disease, having a member of the palliative care team can play a vital role in the holistic management of these complex patients [44-46].

Management of systemic sclerosis-interstitial lung disease

To date, the treatment of SSc-ILD is limited to targeting inflammatory pathways with corticosteroids or alternative immunosuppressive therapy. This therapeutic approach is largely empirical and parallels strategies historically used in treating idiopathic pulmonary fibrosis and related disorders. Cyclophosphamide is currently the most studied immunosuppressive therapy in SSc-ILD, but there remains a scarcity of randomized controlled trials in the literature. To date, only two large randomized controlled trials comparing cyclophosphamide to placebo have been conducted. The first by Tashkin *et al*. (the Scleroderma Lung Study I) showed a small but significant improvement in FVC and quality of life [27]. The second trial by Hoyles *et al.* showed no significant difference in pulmonary function, disease burden on HRCT, or gas exchange between intravenous pulse dose cyclophosphamide *vs.* placebo [47]. A further study looking at the safety and effectiveness of mycophenolate mofetil (MMF) reported that this drug might be beneficial in the stabilization of lung function in SSc-ILD, although the significance and longevity of this benefit remain uncertain [48]. Other single-center studies and case reports have documented stabilization of PFTs and imaging scores with the use of MMF in patients who did not respond to cyclophosphamide, although this difference was only noted in patients with a shorter disease course [49]. Tashkin *et al.* later compared treatment with MMF for 2 years *vs.* cyclophosphamide for 1 year (the Scleroderma Lung Study II). While they noted significant improvement in lung function, they were unable to confirm greater efficacy at 24 months with MMF despite its superior tolerability and toxicity profile [50].

Steroids should be generally avoided in SSc. High-dose corticosteroids and even long-term use of low to moderate dose corticosteroids have been associated with precipitation of scleroderma renal crisis. They should be used in the lowest possible dose for the lowest possible time, only if absolutely needed, such as in inflammatory myositis, refractory inflammatory arthritis, or active inflammatory alveolitis.

Recently, treatment with humanized monoclonal antibodies has added a new alternative to the treatment repertoire. In an EUSTAR cohort study, rituximab was shown to be effective in the improvement of skin fibrosis and prevention of worsening lung fibrosis, supporting the concept of targeting B cells in SSc-ILD [51]. In addition, the RECITAL trial showed that rituximab was non-inferior to cyclophosphamide in SSc-ILD and was associated with fewer adverse effects [52]. Tociluzimab, another monoclonal antibody, has been demonstrated by Khanna *et al*. to help preserve lung function tests in patients with early SSc-ILD and elevated acute phase reactants [53]. Hematopoietic stem cell transplantation (HSCT) has also been considered as a treatment option in SSc-ILD and requires further robust evidence of its benefit, as an observational study by Ciaffi *et al*. failed to show a significant benefit after 12 months following HSCT (n=20) *vs.* cyclophosphamide (n=31), despite a reduction in ILD extent on HRCT scans (in the HSCT group), warranting further prospective data to help decide if HSCT should be considered a treatment option in SSc-ILD [54].

Nintedanib has been approved by the Food and Drug Administration in the USA and National Institute of Clinical Excellence in the UK for treatment of SSc-ILD following randomized trial data indicating that the annual rate of decline in FVC was lower with nintedanib than with placebo at 1 year [55], and it is certainly a signal to consider alternative approach to manage ILD with the combination of anti-fibrotic and anti-inflammatory therapies or nintedanib alone (if the predominant abnormality is fibrosis and patient has not responded to immunosuppression). Indeed, in this trial, there was a suggestion that mycophenolate combined with nintedanib was a more effective strategy than either treatment alone. A post-hoc analysis of the SENSCIS trial showed that patients with SSc-ILD benefit from Nintedanib, irrespective of the extent of fibrotic parenchymal disease at baseline [56].

The findings from the SENSCIS trial suggest that patients with SSc-ILD are at risk of progression, and patients with early scleroderma, extensive skin fibrosis (mRSS 15-40), or elevated inflammatory markers had a more rapid decline in FVC over 52 weeks as compared to the overall trial population [57]. Furthermore, nintedanib was numerically better in the cohort with these risk factors for rapid progression. Hence, only baseline characteristics cannot be used for deciding which patients with SSc-ILD would benefit from nintedanib, but therapeutic decisions should be based on a range of data, such as the presence of risk factors for progression, other manifestations, or co-morbidities, as well as patient preferences.

It is reassuring that nintedanib has demonstrated significant benefit in a broad range of ILDs (including CTD-ILD) with a progressive fibrotic phenotype, supporting the use in a wide variety of ILDs irrespective of the etiology [58]. The findings of the INBUILD trial led to the approval of nintedanib across the world, and it has become a standard of care in progressive pulmonary fibrosis.

The selection of patients for treatment depends on a number of factors, as SSc-ILD can have a variable disease course. A recent Delphi study comprising rheumatologists and respiratory physicians resulted in a consensus statement for the treatment of SSc-ILD. A consensus was made regarding starting patients on treatment who had FVC<80% predicted with abnormal or progressive HRCT, FVC>80% predicted with high-risk patient or notable decline in FVC, dyspnea, or peripheral capillary desaturation on exercise. The panel also agreed not to commence treatment for patients who have had long-standing ILD (10 years) with stable lung function tests and radiological features [59].

When confronted with managing SSc-ILD or ILD in general, we must take into account the disease behavior classification, as it helps to guide treatment goals and monitoring strategies. Firstly, SSc-ILD can manifest as an active but reversible disease with risk of progression, so the treatment goal is to achieve an initial response and observe to monitor persistence of response. Second, it can present as stable but with residual disease, and the goal will be to maintain the *status quo* and monitor in the long term to ensure stability. Third, a proportion of patients may have progressive irreversible disease and potential of stabilization; and goal will be to prevent leading it onto end stage fibrosis and unfortunately, it may not be preventable and at times, despite aggressive treatments (both pharmacological and non-pharmacological), there is progression of ILD with resultant end-stage lung damage; where palliative and supportive care are the only options for management. Furthermore, there is a small window of opportunity when the disease is advanced, and the patient is stable enough to consider a lung transplant as a defin-

itive treatment option, and close liaison with the transplant team is crucial to capture that period in the patient's journey. However, esophageal dysmotility and reflux pose a challenge for lung transplant consideration.

A recent American Thoracic Society clinical practice guidelines on the management of SSc-ILD have made strong recommendations in favor of mycophenolate and conditional recommendations in favor of cyclophosphamide, tociluzimab, rituximab, nintedanib, and a combination of mycophenolate and nintedanib. Furthermore, these evidence-based recommendations suggest further research into the safety and efficacy of pirfenidone as well as the combination of pirfenidone and mycophenolate in the management of SSc-ILD [46].

We propose a simplified algorithm for the management of patients with SSc-ILD for clinicians dealing with SSc and its respiratory complications, and it would be of help to a wide range of disciplines that are involved in the care of this complex patient cohort (Figure 1).

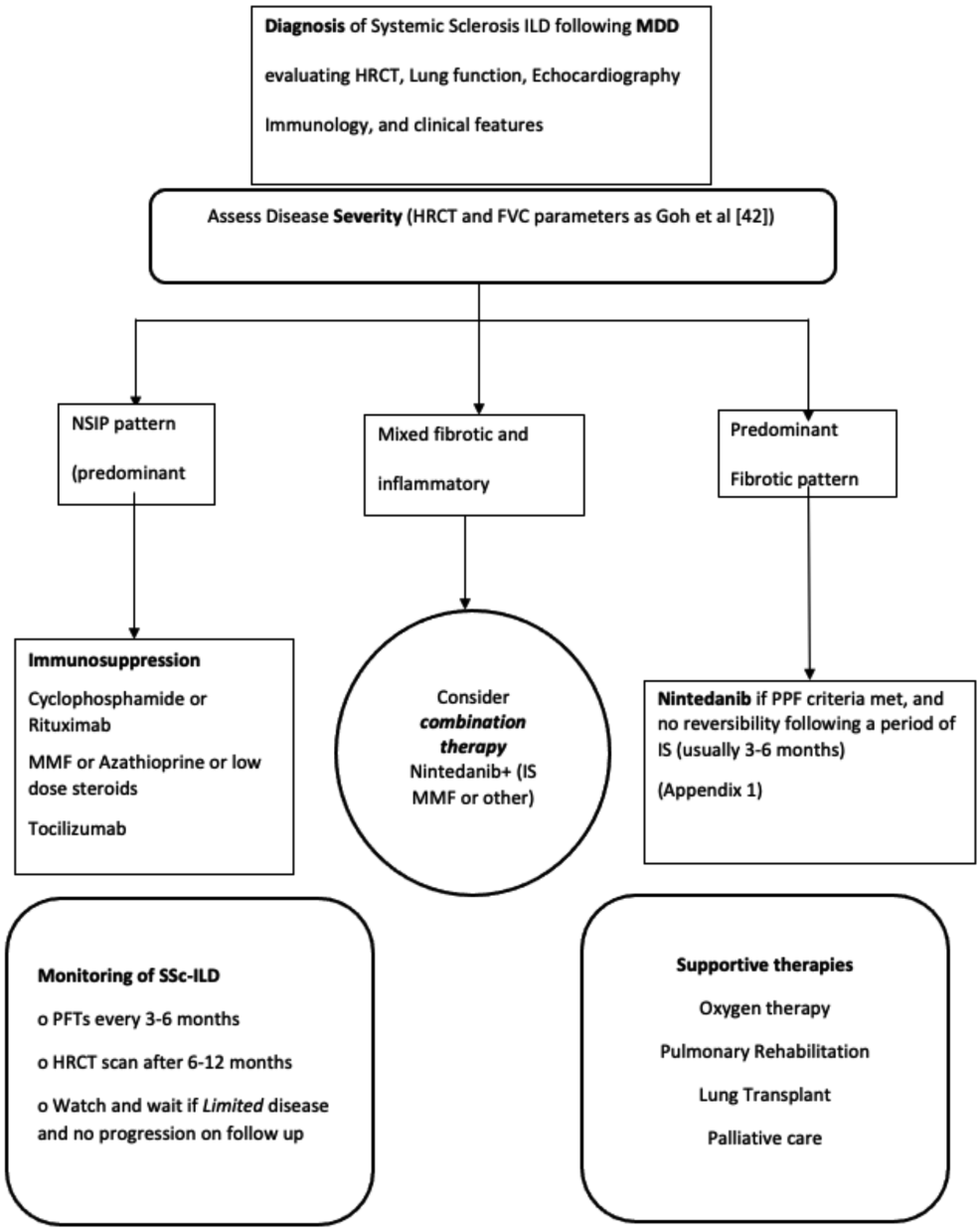

Figure 1. Management algorithm for patients with systemic sclerosis associated with interstitial lung disease after the diagnosis. MDD, multi-disciplinary discussion; HRCT, high-resolution computed tomography; FVC, forced vital capacity; MMF, Mycophenolate Mofetil; IS, immunosuppression; NSIP, non-specific interstitial pneumonia; PPF, progressive pulmonary fibrosis; SSc, systemic sclerosis; ILD, interstitial lung disease.
Appendix 1, progressive pulmonary fibrosis (PPF) criteria as per INBUILD Trial [58]: either one of the following: i) a relative decline in FVC% predicted of at least 10% predicted compared with pre-screening in the past 24 months; ii) a relative decline in FVC% predicted of at least 5% predicted, but less than 10% predicted, with worsening respiratory symptoms or increasing fibrotic changes on high-resolution chest imaging compared with pre-screening in the past 24 months; iii) worsening respiratory symptoms and increasing fibrotic changes on high resolution chest imaging in the past 24 months.

Conclusions

Capturing disease activity in SSc-ILD presents significant challenges. Due to multi-organ involvement and the complex nature of SSc-ILD, multi-disciplinary engagement is the key to providing optimal care to these patients. The combination of HRCT and PFTs is currently used to guide treatment decisions, but this approach has its limitations. Currently, immunosuppressive treatment with cyclophosphamide or MMF is are most prescribed therapy for SSc-ILD, but their effect is modest at best and associated with significant toxicity. Thus, there is a need for better tools and biomarkers for SSc-ILD management. We are likely to witness the expansion of anti-fibrotic therapies such as nintedanib and pirfenidone for the management of SSc-ILD in the near future. It is imperative that we think of balancing the anti-inflammatory *vs.* anti-fibrotic aspect of disease pathogenesis in this complex clinical entity and consider therapeutic options carefully in individual patients, taking into account the contribution of inflammation *vs*. fibrosis when deciding on therapies (immunomodulatory *vs.* anti-fibrotics) along with close multi-disciplinary collaboration.

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