

Management of Scleroderma-Associated Pulmonary Involvement

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Opinion statement

In the absence of a disease-modifying treatment for systemic sclerosis (SSc), the management of the main causes of morbidity and mortality is essential to offer the best possible patient care. Accordingly, early diagnosis and treatment of lung involvement plays a central role. Several new agents against pulmonary artery hypertension (PAH) have driven a notable progress in managing this complication in the recent years. Prostacyclin derivatives, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or guanylate cyclase stimulators are used today in single or combined therapy to improve the prognosis of PAH patients. Regarding interstitial lung disease (ILD) cyclophosphamide remains the most evidence-based therapy for SSc ILD. Small-scale interventional or observational studies support mycophenolate mofetil for either first-line or maintenance

therapy after an initial course of cyclophosphamide. Observational studies also show promising results for biologic agents like Rituximab, and autologous stem cell transplant appears to be an option for severe and carefully selected cases. Moreover, nintedanib and pirfenidone have been shown to be effective in recent studies for idiopathic lung fibrosis. Randomized controlled trials are needed to test the effects of these potential therapies in SSc-ILD. The development of targeted therapies for lung involvement in SSc, together with the increasing knowledge regarding patient selection and management of the available drugs, will help to improve care of SSc patients with lung involvement.

Introduction

Pulmonary involvement, in its two major entities pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD), is frequent in systemic sclerosis (SSc) and represents the most important determinant of SSc-related mortality in the modern management era [1].

PAH is a progressive vascular disorder involving the pulmonary circulation and ultimately causing right heart failure and death [2]. PAH is a rare condition with a prevalence of 15–50/million in the Western countries [3, 4]. Systemic sclerosis (SSc) PAH is the leading cause of connective tissue disease (CTD)-associated PAH, which represents 15–30 % of PAH cases [3, 4]. In SSc, PAH is a rather common complication, with a prevalence of around 10 % [5–7]. In the 2000s in France, the prevalence and yearly incidence of SSc-PAH were 7.85 and 0.61 %, respectively [6, 8]. Despite the development of innovative therapies [9], long-term outcomes are poor, PAH being a leading cause of death in SSc-PAH patients who respond less well to PAH therapy when compared to idiopathic PAH [1, 2, 10].

Interstitial lung diseases represent a heterogeneous group, the two most frequent entities being idiopathic pulmonary fibrosis (IPF) and connective-tissue

associated ILD, among which SSc-ILD has highest frequency [11]. There is no standard definition for SSc-ILD, and due to the different diagnostic methods, the prevalence rates vary considerably across studies. On average, clinically manifest pulmonary fibrosis (PF) in the form of ILD affects about 40 % of patients with SSc [1]. HRCT-defined ILD has been reported with a prevalence of 60–91 % [12], and fibrotic changes in lung parenchyma have been found extensively on autopsy series [13]. ILD is a major cause of morbidity and mortality in SSc patients. According to a recent analysis based on the EUSTAR cohort, lung fibrosis can be accounted for 35 % of SSc-related deaths [14]. Despite the fact that the pathogenesis of SSc-ILD remains incompletely understood, key molecular pathways have been identified, and some progress has also been achieved in the recent years in terms of multidisciplinary disease management, early diagnosis, and prognostic assessment [15]. This progress has led to several novel targeted therapeutic approaches that are currently about to be tested in clinical trials.

In this review, we will focus on the management and treatment of SSc-PAH, its relation to cardiac manifestations, and on the management and treatment of SSc-ILD.

Pulmonary Arterial Hypertension and Heart Involvement in Systemic Sclerosis

Early Detection and Diagnosis

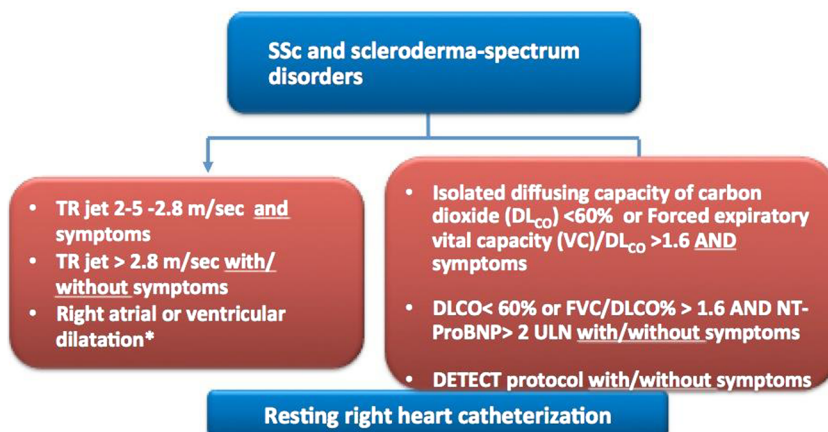
PAH is characterized by a prolonged pre-symptomatic period early in the disease process [16]. The most common initial symptom of PAH is progressive dyspnea with exertion [4]. However, dyspnea is nonspecific and may be confounded by overall dysfunction from SSc disease and concomitant musculoskeletal disease [16]. Signs of right ventricular dysfunction only appear in advanced disease.

Because early PAH detection should translate into improved long-term outcomes, it is widely believed that facilitating early detection or screening is of paramount importance in SSc [17•, 18••]. Of note, some patient's characteristics have been associated with an increased risk of developing PAH (limited SSc, late-age onset, longstanding disease, and reduction in the diffusing capacity of carbon monoxide (DLCO) [18••].

However, screening and early detection of SSc-PAH remain challenging [2, 18••]. Most recommendations attempt to define abnormal transthoracic Doppler echocardiography findings suggestive of pulmonary hypertension. The tricuspid regurgitant jet velocity (allowing to estimate systolic PAP) is the most widely used screening tool [2, 18••, 19]. Although several studies have demonstrated reasonable correlations between estimated systolic PAP and invasive measurements by right heart catheterization (RHC), there are significant limitations to this echocardiographic technique, especially in early disease [2, 18••, 19]. Thus, when pulmonary hypertension is suspected, RHC is of course mandatory to confirm and characterize it [19]. Other parameters such as DLCO, alone or in combination with NT-proBNP, have been used in some screening programs by clinicians [18••]. Recently, the DETECT study group published the first screening study to undertake systematic RHC in a cohort of SSc patients for diagnosis of PAH [20•]. This analysis suggested a stepwise algorithm using clinical data and noninvasive tests for earlier identification of PAH in an SSc population with a higher risk of developing PAH (DLCO < 60 % and SSc diagnosed since at least 3 years). The DETECT algorithm recommended RHC in 62 % of patients (referral rate) and missed 4 % of PAH patients (false negatives) [20•]. By comparison, applying ESC/ERS guidelines to these patients, 29 % of diagnoses were missed while requiring an RHC referral rate of 40 % [2, 20•]. Based on current knowledge, a group of experts suggested that screening pulmonary function tests with single breath DLCO, transthoracic Doppler echocardiography, and measurement of NT-proBNP should be performed in all patients with SSc as soon as any new signs or symptoms suggestive of pulmonary hypertension develop; further, they considered that DLCO and Doppler echocardiography should be performed annually in all SSc patients. [18••] This approach is illustrated in Fig. 1. The proceedings of the Fifth World Symposium on Pulmonary Hypertension (Nice, 2013) indicated that (i) annual screening for PAH is recommended in (cardiopulmonary) asymptomatic patients with the SSc spectrum of diseases, although there is a lack of evidence-based data; (ii) screening of patients with the SSc spectrum of diseases without clinical signs and symptoms of PH should include a two-step approach using clinical assessment for the presence of telangiectasia, anticentromere antibodies, PFT and DLCO measurements, electrocardiogram, and biomarkers (NT-proBNP and uric acid) in the initial stage, followed by echocardiography and consideration of RHC in patients with abnormal findings, although there is a lack of data with DLCO > 60 %; and (iii) the above-mentioned screening programs for patients with SSc should be part of a scientific protocol, or a registry, whenever possible [19].

A definite diagnosis of SSc-PAH also requires exclusion of other causes of pulmonary hypertension such as left heart and/or chronic lung disease [2, 19]. In PAH, RHC will demonstrate an elevated mean pulmonary artery pressure (PAP) > 25 mmHg, a pulmonary capillary wedge pressure < 15 mmHg, and pulmonary vascular resistance > 3 Wood units [21].

Recommendations—Referral for RHC



Symptoms: dyspnea on rest or exercise, fatigue, pre-syncope/ syncope, chest pain, palpitations, dizziness, lightheadedness.

Signs: Loud pulmonic sound, peripheral edema

*Right atrial (>53 mm) or ventricular enlargement (>35mm)

Fig. 1. Consensus-based approach for screening for PAH in patients with connective tissue diseases (adapted from Khanna et al. [18••]).

Cardiac Involvement and its Relation to PAH

In addition to vascular involvement, other vital organs are commonly affected in SSc. Heart involvement affects the myocardium, pericardium, and/or small vessels [22–25]. Myocardium involvement includes fibrosis and impaired microcirculation in around half of SSc patients, leading to left heart disease with a high reported prevalence of a range of abnormalities detected by echocardiography including left ventricular hypertrophy, diastolic left ventricular dysfunction, and left atrial enlargement. Pericardial effusion is also more common in SSc-PAH, as compared to idiopathic PAH [16]. Effusions may be due to progressive right heart failure and/or to the underlying inflammatory processes. In addition, conduction abnormalities and hormonal and metabolic dysfunctions (elevated NT-proBNP and hyponatremia) are more common in SSc-PAH as compared to idiopathic PAH [16]. Of note, SSc-PAH patients typically have less severe hemodynamic impairment compared to idiopathic PAH [16, 26].

Right ventricle adaptation to the increased cardiac load is the main determinant of outcome in PAH [27]. Importantly, right ventricle contractility is lower in patients with SSc-PAH than in idiopathic PAH, supporting that right ventricle systolic dysfunction is more common in SSc [28]. Thus, inability of the right ventricle to compensate for higher afterload (rather than differences in afterload) may explain at least in part SSc-PAH worst outcomes.

Approved and Novel Therapies of SSc-PAH

Basic treatment of SSc-PAH includes supplemental oxygen in patients who are hypoxic at rest or with exercise, diuretics for the management of volume overload and right heart failure, and digoxin for right heart failure complicated by atrial arrhythmias [10]. Although widely used in patients with SSc for treatment of Raynaud's phenomenon, there is little role, if any, for calcium

channel blockers in the treatment of SSc-PAH [29]. There are no robust data on the role of anticoagulation in SSc-PAH. The analysis of a recent registry has suggested that anticoagulation was associated with a survival benefit in patients with idiopathic PAH but not in patients with SSc-PAH [30]. Indeed, the risk of bleeding is higher in SSc-PAH when compared to idiopathic cases [31].

Several drugs have been approved for PAH in recent years [32]. These agents target endothelial cell dysfunction with prostacyclin derivatives, endothelin receptor antagonists, and agents improving the defective nitric oxide pathway (phosphodiesterase type 5 inhibitors or guanylate cyclase stimulators) [32]. In SSc-PAH, continuous intravenous epoprostenol improves exercise capacity and hemodynamics compared with conventional therapy [33]. However, the need for continuous infusion, meticulous catheter care, and daily preparation of the medication can be challenging in patients whose manual dexterity may be impaired by scleroderma. Other prostacyclin analogues such as subcutaneous, nebulized, or intravenous treprostinil or iloprost can be used in SSc-PAH [32]. PAH treatment with dual endothelin receptor antagonists (bosentan and macitentan) or selective endothelin-A receptor antagonist (ambrisentan) improves functional class, exercise capacity, time to clinical worsening, and hemodynamics in PAH. Of note, macitentan has been shown to improve a combined morbidity/mortality primary endpoint in a large event-driven study [32–34]. In subgroup analyses of patients with SSc-PAH, similar trends were observed, and these agents are approved for treatment of SSc-PAH. Safety signals include liver transaminase elevations with bosentan, hemoglobin level reduction with macitentan, and peripheral edema with ambrisentan [32–34]. Sildenafil, a phosphodiesterase type 5 inhibitor that reduces the catabolism of cGMP, leading to enhanced effects of nitric oxide, has been widely employed in the treatment of PAH [35]. Improvements in 6-min walking distance, functional class, and hemodynamics after 12 weeks have been described in PAH and CTD-PAH [36]. Similarly, tadalafil studies reported statistically significant improvements in exercise capacity although the proportion of patients with SSc was not reported [37]. Riociguat, a stimulator of soluble guanylate cyclase, significantly improved exercise capacity in patients with PAH including CTD-PAH (the proportion of CTD patients with SSc was not reported) [38].

Combination therapy has become common practice in the management of PAH [32],[39]. While sequential combination therapy has been convincingly tested in many studies and adopted in published guidelines, the exact positioning of upfront combination therapy in PAH-SSc remains debated [32, 40].

While imatinib demonstrated improvements in hemodynamic measurements in phase II/III studies, imatinib is neither approved nor recommended in PAH because of a number of severe bleeding episodes (subdural hematomas) [32, 41]. Given the potential role of autoimmunity in the pathogenesis of SSc-PAH, a randomized clinical trial of rituximab, an anti-CD20 therapy that depletes B-cell lineages, is specifically and exclusively enrolling SSc-PAH patients who are already on concomitant PAH therapy to assess hemodynamic response [32].

Despite the advances in medical therapy for PAH, lung transplantation remains the ultimate therapeutic option for many eligible PAH patients [2, 32]. SSc multiorgan involvement increases perioperative and postoperative risk. In particular, esophageal dysmotility increases markedly the risk of aspiration and posttransplant dysfunction. Clinical and subclinical renal disease may also

increase complications related to the use of nephrotoxic immunosuppressive agents. For these reasons, SSc-PAH patients are often denied lung transplantation. However, eligible patients with SSc have similar rates of survival after lung transplantation compared with patients with pulmonary fibrosis or idiopathic PAH [42, 43•].

Inflammation and autoimmunity are recognized as important factors in PAH and may be future treatment targets [16, 44–47].

Investigation, Prognostic Evaluation, and Monitoring of Systemic Sclerosis–Interstitial Lung Disease (SSc-ILD)

The Identification of SSc-ILD

As there is no current consensus on a routine screening protocol [e.g., pulmonary function tests (PFTs), high-resolution computed tomography (HRCT)], clinicians often base investigation on symptoms (which are highly nonspecific) and chest radiography (which is notoriously insensitive) [48]. Exercise intolerance is usually multifactorial, with variable contributions from SSc-ILD, SSc-PAH, cardiac involvement, musculoskeletal involvement, fatigue, weight gain, and loss of fitness. In occasional patients, it is helpful to reproduce exertional dyspnea by means of a 6-min walk test or maximal exercise testing on room air. The absence of oxygen desaturation at the limit of exercise tolerance excludes major cardiopulmonary limitation.

SSc-ILD is present on HRCT in over 50 % of SSc patients and in over 90 % of SSc patients with abnormal PFTs [49, 50]. HRCT appearances usually consist of a variable combination of ground-glass attenuation and fine reticulation. Honeycombing is present in a minority, but in a series of over 200 patients with SSc-ILD, HRCT appearances were, on average, identical to those in idiopathic nonspecific interstitial pneumonia (NSIP) [51]. Atypical HRCT appearances should alert the clinician to concurrent disease processes (e.g., smoking-related interstitial lung disease, drug-induced lung disease) with consolidation (typically seen in lung disease in inflammatory myopathy [52]), suggesting an underlying overlap syndrome or, when it is unifocal and does not regress with time, lung adenocarcinoma. Ground-glass attenuation on HRCT tends to be reversible when present in isolation, but this presentation is infrequent. More often, ground glass is admixed with a reticular pattern [53] or associated with traction bronchiectasis [54], represents fine intra-lobular fibrosis, and seldom regresses on serial HRCT [55].

PFTs are not sensitive in the early identification of SSc-ILD. An unequivocally restrictive ventilatory defect is strongly indicative of lung involvement. However, in early disease, forced vital capacity (FVC) values often lie within the normal range (of 80–120 % of predicted from age, gender, and height). For example, a measured FVC value of 85 % in an individual patient might be “normal” for that patient, but might also represent a major decline of a premorbid value of 110–120 %. The DLCO is more sensitive but is also influenced by pulmonary vascular limitation and smoking-related damage [56]. It has long been concluded that isolated abnormalities in bronchoalveolar lavage cellularity are not predictive of the subsequent development of SSc-ILD.

The Evaluation of the Clinical Significance of SSc-ILD

The sensitivity of HRCT not only offers major advantages but also poses problems, due to the detection of nonprogressive subclinical abnormalities. In a series of over 200 consecutive SSc-ILD patients, interstitial abnormalities were trivial or very limited in extent in over 40 % of cases. The integration of HRCT appearances and PFTs are central to the accurate characterization of disease severity. SSc-ILD is characterized by a restrictive defect and a reduction in DLCO [56]. In the absence of SSc-PAH, arterial oxygen levels tend to be well preserved until lung disease is advanced. PFT are strongly predictive of outcome in SSc [57–59] and SSc-ILD [60] alike. DLCO levels correlate better than other PFT with disease extent on HRCT [61], reflecting the fact that DLCO captures the total combined impact of SSc-ILD on alveolar volume and pulmonary blood volume.

A final judgment on the clinical significance of SSc-ILD is essentially a multidisciplinary exercise in which symptoms, PFTs, HRCT appearances, and findings on echocardiography are integrated. The means by which this is done is not an exact process, but one in which the clinician seeks plausibility and consistency across the four domains. The first step is to quantify severity more accurately than is possible with a single variable, and the second step is to understand the determinants of severity. Sometimes, it becomes obvious, based on HRCT evaluation and echocardiography that symptoms and functional impairment result primarily from smoking-related damage or SSc-PAH and not from SSc-ILD.

Prognostic Evaluation in SSc-ILD

It is uniformly accepted that immediate treatment is not warranted in asymptomatic patients with SSc-ILD that is obviously “clinically insignificant”. It is also widely agreed that treatment should be instituted when there is major inflammatory or progressive fibrotic lung involvement. However, many patients with SSc-ILD lie between these two poles. When lung disease is mild to moderate (i.e., not subclinical), careful observation without intervention can often be justified. However, such decisions are not always easy. Studies of outcome in lung disease in connective tissue disease mostly consist of SSc data. Due to a lack of definitive evidence, current prognostic evaluation, summarized in a recent review [62••], is based equally on cohort studies and a traditional mixture of accumulated clinical experience, logic, and common sense. As no single variable consistently predicts disease progression, it has been argued that three important general factors should be considered [62••], as shown in Table 1.

First is the duration of systemic disease. The view that SSc-ILD is more likely to progress early in the course of systemic disease is based on accumulated clinical experience including the data of Steen [57, 63]. It appears that progression occurs much more frequently in the first 2 years of systemic disease and especially when the onset of lung disease precedes the cutaneous manifestations of SSc.

Second is the disease severity. The threshold for instituting therapy is much lower in severe disease for two reasons. By its very presence, severe disease implies that progression has occurred repeatedly in the past and is likely to continue, if untreated. Equally important is the fact that when a patient has a

Table 1. The prediction of progression of pulmonary disease in relation to individual variables: the past, the present, and the likely future

Currently important	Disease severity (FVC, HRCT) Duration of systemic disease Ongoing disease progression
Desirable but not routinely used	Serum biomarkers Genetic associations
Historical tests, now discarded	Histological pattern at lung biopsy Bronchoalveolar lavage

very poor respiratory reserve, failure to prevent disease progression may have catastrophic effects on quality of life. However, as treatment decisions are dichotomous (i.e., to treat or to observe), key severity thresholds on which to base management are needed by clinicians. The first SSc-ILD staging system, the UK Raynauds and Scleroderma Association (UKRSA) staging system, was based on optimal HRCT and FVC thresholds, validated against mortality [64]. In essence, disease is categorized as “mild” or “extensive” when it is immediately obvious on rapid HRCT evaluation that SSc-ILD occupies less than (mild) or more than (extensive) 20 % of the total lung volume. In cases considered to be indeterminate on HRCT, an FVC threshold of 70 % is used. The prognostic value of the UKRSA value system has been confirmed [12], and it is reassuring that similar HRCT and FVC thresholds were predictive of disease progression in the placebo arm of the Scleroderma Lung Study of oral cyclophosphamide in SSc-ILD [65].

Third is the ongoing progression. Strangely, the prognostic value of disease progression against subsequent mortality has yet to be definitively evaluated in SSc-ILD, although well established in IPF [66]. However, based on analogies with other interstitial lung diseases, it is universally accepted that evidence of recent disease progression is an indication for therapy.

It appears that most clinicians favor the introduction of therapy when two of three adverse prognostic factors are present. However, such decisions are often very close calls, and patient preferences often dictate an initial policy of careful observation at three to six monthly intervals, with immediate intervention in the event of disease progression. A prognostically accurate biomarker would greatly facilitate management: Preliminary data suggests that serum levels of KL-6, SP-D, or IL6 [67–71] may provide added value, but no serum biomarker is currently validated.

Monitoring SSc-ILD

Unless disease progression is major, no single method of detecting change (symptoms, PFT trends, and HRCT change) is uniformly reliable. Symptomatic change is often misleading: The multifactorial nature of exertional dyspnea, discussed earlier, is further confounded by low-grade infection, especially in patients receiving immunosuppressive therapy. Serial pulmonary function tests are central to routine monitoring but must be reconciled with clinical information and, in selected patients, serial HRCT evaluation. Based on studies of

the reproducibility of PFTs in healthy subjects, a change from baseline in FVC or DLCO of 10 or 15 %, respectively, is viewed as evidence of true change, not ascribable to measurement variation. However, serial estimation of both FVC and DLCO allows earlier detection of disease progression. Concordant decline, even when not reaching threshold values (e.g., a reduction in FVC of 9 %, a reduction in DLCO of 13 %), is strongly indicative of true change. Serial HRCT should not be performed routinely by protocol, due to radiation constraints, but should be reserved for specific clinical questions (e.g., a change in disease severity is suspected but is uncertain due to discrepancies between other serial variables).

Early in the course of disease, repetition of FVC and DLCO at three to six monthly intervals is appropriate, with the exact timing influenced by baseline disease severity. In patients with SSc-ILD that has been stable for over 12 months, the time interval between serial PFTs can be gradually increased, but unless SSc-ILD is truly subclinical, annual PFT monitoring should continue in the long term.

Management of Systemic Sclerosis–Interstitial Lung Disease

The current treatment of SSc-ILD is mostly based on immunosuppressive agents. Recent randomized clinical trials (RCTs) allowed shifting from early empirical approaches towards an increasingly evidence-based therapeutic management of SSc-ILD. However, many open questions still have to be addressed until high-quality treatment recommendations for SSc-ILD can be developed.

One of the key steps towards a better management of SSc-ILD treatment is to identify which patients are likely to respond to the selected therapy. The duration and dosage of the immunosuppressive treatment relies largely on expert opinion and on the individual case characteristics—most importantly on drug tolerability and therapeutic response [72].

In the following paragraphs, we will focus on the main therapeutic agents currently in use for the treatment of SSc-ILD and introduce potential perspectives for future therapies.

Cyclophosphamide

The European League for Rheumatology (EULAR) treatment recommendations state that CYC should be considered for the management of SSc-ILD [72]. These recommendations are based on two prospective, double-blind, placebo-controlled RCTs, the Scleroderma Lung Study (SLS) and the Fibrosing Alveolitis in Scleroderma Trial (FAST) [65, 72, 73]. Both studies found a positive improvement in lung function at 12 months in the CYC treatment group. The favorable difference in FVC% change between the treatment and placebo group was nevertheless modest with 2.5 % in SLS [65] and 4.2 % in FAST [73]. There was also significant, but overall mild beneficial effect on additional outcomes such as the Mahler dyspnea index, modified Rodnan skin score, health-related quality of life, and an HRCT fibrosis score [74].

Notably, the effects on these outcome measures appeared to be transitory and disappeared 1 year after treatment discontinuation in the open-label extension of the SLS study [65, 75, 76]. However, most of the patients in the open-label extension study did not receive maintenance therapy. These results highlight the need for a long-term management strategy after discontinuation of CYC [76]. Unfortunately, controlled studies analyzing the effects of different maintenance therapies such as azathioprine or mycophenolate mophetil (MMF) after CYC treatment are not available. In addition, the optimal treatment duration with CYC is not known [77].

The route of CYC administration, either oral or intravenous (IV), largely depends on local availability and traditional use. Various studies report beneficial effects from both approaches, but there is limited data comparing the benefits and safety profile of these two routes of administration in SSc patients [78]. In SSc-ILD, IV pulse therapy is considered to have a lower risk for hemorrhagic cystitis and, most likely, also for bladder cancer, compared to long-term oral CYC therapy [73, 79]. On the other hand, a report comparing adverse events in patients with systemic autoimmune diseases treated with IV or oral CYC shows a higher frequency of gastrointestinal discomfort (nausea, vomiting, abdominal pain, and diarrhea), alopecia, and dizziness in the IV group [80]. Overall, the most frequent adverse effects reported in SSc-ILD patients undergoing CYC treatment are nausea and vomiting [81, 82] or mild leukopenia (responsive to dose reduction) [82]. The main reasons for treatment discontinuation were hemorrhagic cystitis, pneumonia, intolerable nausea, and worsening PFTs [82].

Having in mind the significant side-effect profile and the overall modest clinical benefit, it is important to select the adequate patients for therapy with CYC. A retrospective analysis of the SLS identified that patients with extensive reticular changes on HRCT (>50 %) and/or a high mRSS (>23 points) at baseline had a twofold higher benefit from CYC treatment (as reflected by the decrease in FVC% predicted) at 12 and 18 months [83]. These findings still need validation in prospective studies but, nonetheless, could allow a more evidence based selection of patients for CYC treatment, thus maximizing the therapeutic benefit and avoiding unnecessary use of a potentially toxic agent.

In our clinical practice, if we decide to treat patients with CYC, we use IV pulse therapy for 6 months and continue with MMF or azathioprine maintenance therapy. In general, we only use low-dose corticosteroids because of the association of medium and high-dose corticosteroids with renal crisis.

Mycophenolate

The number and quality of studies available for MMF and thus the clinical evidence for the efficacy of MMF is lower than for CYC. Nevertheless, several reports from small case series describe a positive outcome in SSc-ILD patients treated with MMF, with stabilization or mild improvement of PFTs and HRCT fibrosis after 6 up to 24 months of therapy [84–88]. Stabilization of lung function has also been observed in a recent, uncontrolled, prospective study including early, immunosuppressive therapy-naïve dcSSc patients, with a median treatment duration of 18 months [89]. Similarly, a retrospective study on 98 patients treated with MMF has shown stable PFTs [90].

Accordingly, a retrospective controlled trial including a large cohort of 109 MMF-treated patients showed a lower frequency of clinically significant lung fibrosis (defined as a $\geq 15\%$ reduction in FVC from baseline or $FVC < 55\%$) and a better 5-year survival in patients receiving MMF compared to other immunosuppressives [91].

Mycophenolate sodium (MS), a related compound, was also shown to stabilize SSc-ILD after 12 months of treatment in a recent, small-scale, prospective study [92].

These reports suggest that MMF or MS treatment is well-tolerated in patients with SSc-ILD [85, 89, 92, 93]. Frequently reported side effects are gastrointestinal disorders, lymphopenia, or infections [89].

However, it is still to be proven whether MMF or MS is superior to placebo and how it performs in comparison to CYC. A recent small, case-control, longitudinal study in SSc-ILD showed significant worsening of HRCT findings in the MMF group compared to CYC-treated patients; no significant differences regarding PFTs were found [87]. The ongoing double blind RCT Scleroderma Lung Study II (NCT00883129), which includes an oral CYC and an MMF arm [94], will hopefully shed light on the comparative performance and tolerability of these agents.

Other Emerging Treatments—Biologics and Stem Cell Transplantation

Several targeted therapies with different biologics have recently been tested in SSc-ILD. Following smaller uncontrolled studies, a recent multicenter, nested case-control, observational study on the EUSTAR cohort showed that patients with SSc-ILD treated with rituximab (RTX) had significantly less decline of FVC compared with matched controls ($N=9$; $0.4 \pm 4.4\%$ vs $-7.7 \pm 3.6\%$; $p=0.02$). These promising results need to be confirmed in RCTs, but support the rationale for RTX therapy in SSc-ILD [95•]. A double-blind RCT comparing RTX to CYC in CTD-ILD is ongoing (NCT01862926).

A preliminary exploratory analysis from the Tocilizumab (TCZ) phase 2/3 RCT “faSScinate” (NCT01532869) showed a reduced frequency of FVC decline in the TCZ-treated group compared to placebo (3 vs 27% with a decline in $FVC \geq 10\%$, $p=0.009$) [96]. FVC was an exploratory outcome in this trial.

Human autologous stem cell transplantation (HSCT) represents an untargeted, more global therapeutic approach. Three controlled trials on HSCT in SSc have been published so far [77]. The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) Trial revealed that HSCT-treated patients had significant better long-term event-free survival (defined as death or major organ failure), with the cost of a higher treatment-related mortality in the first year after therapy. At baseline, 87% of patients in the HSCT arm and 80% of patients in the CYC arm had SSc-ILD as diagnosed by HRCT. Mean changes in lung function parameters from baseline until 2 years' follow-up showed a significant amelioration in the HSCT treated group versus the CYC group [97••]. Given its high treatment-related mortality, we consider HSCT as a treatment option in selected cases with very poor prognosis. An ongoing

RCT, the STAT trial (NCT01413100), also including 2 years of post-transplant maintenance therapy with MMF, is under way.

Recent Advances in the Treatment of IPF and Their Translational Potential to SSc-ILD

SSc-ILD and IPF are inherently related and, given their rarity, cross-over research is highly informative. The SSc-ILD phenotype differs from IPF in various aspects including the overall slower decline in lung function, presence of ground-glass infiltrates on HRCT, correlation with autoantibody status, histological evidence of NSIP in contrast to the usual interstitial pneumonia (UIP) seen in IPF, as well as the occasional regression and response to immunosuppressive drugs [98]. Recently, two RCTs in IPF have been published with positive results: Nintedanib, a tyrosine-kinase inhibitor, significantly reduced the annual rate of decline in FVC vs placebo [99•]. Pirfenidone reduced the frequency of progression (≥ 10 % decline in FVC or death) by 48 % at 52 weeks as compared to placebo [100•]. Future trials testing these agents in SSc-ILD are needed.

Conclusion

The recent years have brought important advances in the clinical and therapeutic management of SSc lung disease. Early diagnosis, improved patient selection, and monitoring are key elements to consider in the current management of SSc lung disease. Alongside, new targeted therapies and agents with an improved safety profile are under development.

Compliance with Ethics Guidelines

Conflict of Interest

Rucsandra Dobrota reports grants from Pfizer and Actelion, outside the submitted work.

Oliver Distler has/had consultancy relationship and/or has received research funding in the area of systemic sclerosis and related conditions from Actelion, Pfizer, Ergonex, BMS, Sanofi-Aventis, United BioSource, Roche/Genentech, Medac, Biovitrium, Boehringer, Novartis, 4D Science, Active Biotec, Bayer, Sinoxia, Serodapharm, EpiPharm, Biogen, Pharmacyclics, Inventiva, and GSK.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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