Interstitial lung disease: how should therapeutics be implemented?

Bruni, C.; Campochiaro, C.; Vries-Bouwstra, J.K. de

Interstitial Lung Disease
How Should Therapeutics Be Implemented?

Cosimo Bruni, MD, PhD[a,b,*,1], Corrado Campochiaro, MD[c,1], Jeska K. de Vries-Bouwstra, MD, PhD[d]

KEYWORDS

• Systemic sclerosis • Interstitial lung disease • Combination therapy
• Targeted therapies • Treatment

KEY POINTS

- Interstitial lung disease (ILD) is highly prevalent in systemic sclerosis (SSc) and associated with morbidity and mortality.
- SSc-ILD course is highly variable and prediction at the individual patient level is challenging.
- Evidence-based guidelines on the definition of clinically relevant progression of SSc ILD, and on the content and timing of monitoring SSc-ILD patients are urgently awaited.
- Recently, important new treatment options have become available that contribute to improved treatment of SSc-ILD.
- How to best apply these drugs, in terms of timing, and mono versus combination, needs to be determined in the coming years.

INTRODUCTION

Interstitial lung disease (ILD) is a frequent organ manifestation in systemic sclerosis (SSc) and is associated with high morbidity and mortality. Reported prevalence varies between 35% and 75% of patients with SSc, depending on the patient selection and definitions applied.[1–3] Importantly, SSc-ILD is a leading cause of morbidity and mortality in SSc,[4,5] determining a mortality risk nearly three times greater than in SSc patients without ILD,[6] particularly in youngers and in males.

[a] Department of Rheumatology, University Hospital Zurich, University of Zurich, Schmelzbergstrasse 24, Zurich 8006, Switzerland; [b] Division of Rheumatology, Department of Experimental Medicine, Careggi University Hospital - University of Florence, Florence, Italy; [c] Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Via Olgettina 60, Milan, Italy; [d] Department of Rheumatology, Leiden University Hospital, Postal Zone C1-R, PO Box 9600, Leiden 2300 RC, the Netherlands
[1] Equal contribution as first author.
* Corresponding author.
E-mail address: cosimo.bruni@usz.ch
Twitter: @CosimoBruni (C.B.); @CampochiaroCor (C.C.)

Rheum Dis Clin N Am 49 (2023) 279–293
https://doi.org/10.1016/j.rdc.2023.01.005
rheumatic.theclinics.com

High-resolution computed tomography (HRCT) is to date the gold standard for ILD diagnosis.[7] HRCT has been shown to be superior to pulmonary function testing (PFT) in detecting SSc-ILD.[8] Of all SSc patients with typical ILD changes on HRCT, only a minority will show a clear restrictive pattern with PFT.[1] Given the high prevalence and its association with worse prognosis it is recommended to screen each SSc patient by HRCT for ILD at SSc diagnosis, also in the absence of specific respiratory symptoms.

The severity and course of SSc-ILD varies widely, from mild and stable to severe and rapidly progressing.[9] Overall, 20% to 30% of SSc-ILD patients will show the progression of ILD over time, whereas approximately 50% of patients will show a stable disease course and some even show improvement in lung function over time (**Fig. 1**).

Paramount to identify ILD progression and characterizing clinical phenotypes of progressive SSc-ILD is reaching a consensus on how to define progression, considering the various definitions currently available.[10–12] Probably, a multidimensional definition including symptoms, functional assessments, and imaging might best capture clinically relevant progression.

When a patient is diagnosed with SSc-ILD, starting immunomodulatory therapy should be considered based on functional impairment, complaints, and extent of ILD on HRCT.[13]

Although increasing, the number of possible drugs that have proven efficacy in the treatment of SSc-ILD is still limited. Efficacy of cyclophosphamide (CYC) has been shown in two high-quality randomized controlled trials (RCTs) and, therefore, CYC is included in current recommendations for the treatment of SSc-ILD.[14–17] A third high-quality RCT evaluated the efficacy of mycophenolate mofetil (MMF) with oral CYC as a comparator and showed comparable efficacy of MMF and CYC in improving pulmonary function (reflected by Forced Vital Capacity; FVC), complaints, and extent of ILD on HRCT.[18] Use of MMF for SSc-ILD was further substantiated by a post hoc study comparing SSc-ILD patients on placebo that participated in the RCT evaluating CYC (SLS I) with those treated with MMF in the trial comparing CYC and MMF (SLS II). Here, treatment with MMF resulted in significant improvement in lung volumes and dyspnea as compared with placebo.[19] For a selected subgroup of patients with SSc-ILD, hematopoietic stem cell transplantation (HSCT) could be considered. Three RCTs have confirmed the superior efficacy of HSCT in improving FVC as compared with intravenous CYC.[20–22] In addition, few data suggest that treatment with HSCT might even

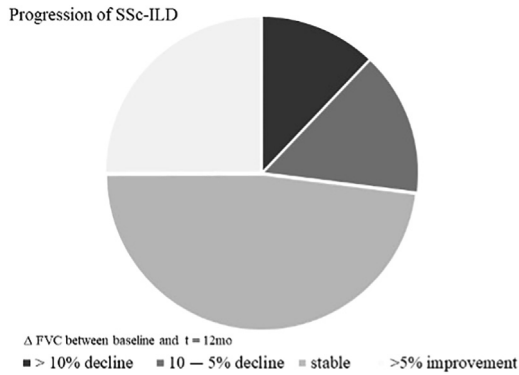

Fig. 1. Progression of SSc-ILD over 12 months in the EUSTAR cohort (9). FVC, forced vital capacity; ILD, interstitial lung disease; SSc, systemic sclerosis.

decrease fibrosis extent on HRCT.[20,23] In view of the risks associated with this strategy, not all SSc-ILD patients are candidates for HSCT, which could be considered in a subgroup of patients with diffuse skin disease and rapid disease progression. Recently, tocilizumab and nintedanib have been added to the treatment arsenal for SSc-ILD based on RCT evidence[24,25]: these will be addressed in the section below, together with a discussion on the positioning of the different drugs available for the treatment of SSc-ILD. As a last option, when the situation is deteriorating despite maximum pharmacological and non-pharmacological efforts, lung transplantation should be considered, and patients should be referred to a transplantation center.[26]

The variable course of SSc-ILD, the complexity in determining and predicting the progression of SSc-ILD, and the limited but highly diverse treatment options for SSc-ILD, pose many challenges for everyday clinical practice (**Fig. 2**). In this review, we discuss the currently available evidence for treatment together with areas where additional evidence is highly warranted. In the meantime, multidisciplinary team care involving experts from rheumatology, pulmonology, and radiology is recommended to offer SSc-ILD patients high-quality care following the most recent insights.[27]

DISCUSSION

Selection of Patients

Risk factors for the presence of systemic sclerosis-interstitial lung disease

First challenge in clinical practice is to identify the patients with SSc-ILD. Given the high prevalence and its association with a worse prognosis, it is recommended to screen each SSc patient by HRCT for ILD at the time of SSc diagnosis, also in the absence of specific respiratory symptoms. In support, to determine the urgency and timing of performing the HRCT, several clinical characteristics have been associated with presence of SSc-ILD (**Fig. 2**). Impaired lung function at the time of SSc diagnosis and respiratory symptoms like cough and dyspnea are associated with ILD presence. Also male gender, presence of anti-topoisomerase antibodies (ATA), the diffuse skin type as well as the higher extent of skin involvement evaluated by the modified Rodnan Skin score (mRSS) have been associated with presence of

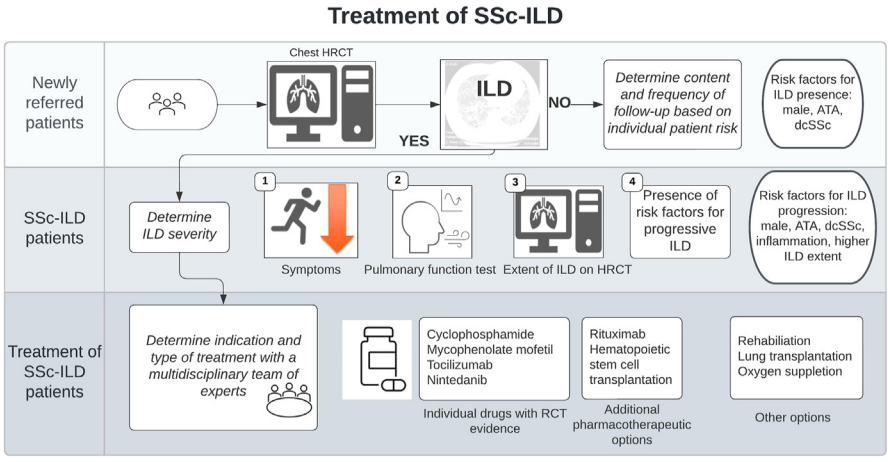

Fig. 2. Overview of the treatment of SSc-ILD. ATA, anti-topoisomerase antibody; dcSSc, diffuse cutaneous SSc; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; SSc, systemic sclerosis.

ILD.[28–33] In addition, other organ manifestations such as gastroesophageal reflux disease, digital ulcers, and pulmonary hypertension (PH) have been linked to the presence of ILD.[34,35] ILD has also been described to be associated with non-Caucasian and African American race.[36] In contrast, presence of anti-centromere antibodies (ACA) is associated with a lower risk for presence of ILD. Nonetheless, It is important to realize that also lcSSc patients and ACA can have ILD.[1,37]

Risk factors for the progression of systemic sclerosis-interstitial lung disease

Once presence of SSc-ILD is confirmed, the next challenge is to determine the content and frequency of monitoring for possible progression (**Fig. 2**). Among patients who do experience ILD progression, the rate of progression can be either rapid or slow.[9] Only a small subgroup of patients, about 8%, will show rapid progression of ILD. It is however paramount to identify this subgroup early as these patients typically experience rapidly increasing parenchymal lung changes leading to a substantial loss of lung function early in their disease course.[9] Clinical risk factors for rapid progression of SSc-ILD include diffuse skin involvement, presence of ATA, increased CRP, worse PFT at baseline, and higher ILD extent on HRCT.[38] These clinical factors can help to customize adequate and timely follow-up of SSc-ILD. In addition, in patients with SSc-ILD and clinical worsening with symptoms like dyspnea and cough, re-evaluation of SSc-ILD is warranted.

Selection of Medications

Thanks to the results of two recent phase III randomized placebo-controlled trials[24,25] showing the efficacy of tocilizumab and nintedanib, the therapeutic armamentarium now available for SSc-ILD has significantly increased. In fact, nintedanib has been approved by the FDA and the EMA for the treatment of SSc-ILD, while tocilizumab by FDA for the same indication.

Nintedanib, a multi-tyrosine kinase inhibitor that blocks FGF receptor-1, VEGF receptor-2, and PDGF receptor-α and β52,[39] was approved for the treatment of idiopathic pulmonary fibrosis in 2014[40] and has become the first treatment approved for the treatment of SSc-ILD after the publication of the largest phase III RCT in SSc-ILD.[24] The SENSCIS trial randomized SSc-ILD patients with a disease duration < 7 years, regardless of their cutaneous disease subset, but with an SSc-ILD extent >10% on HRCT, to receive oral nintedanib 150 mg twice daily or placebo (**Table 1**). This protocol allowed concomitant immunosuppression and 48% of patients were on stable MMF therapy at baseline. Over the study period, the adjusted annual rate of change in FVC was significantly lower in the nintedanib compared with the placebo group ($-$52 mL/year versus $-$93 mL/year, $p = 0.04$). The combination of MMF plus nintedanib gave signals as the best scenario for the prevention of decline. The most common adverse event reported was diarrhea (76% of patients) which was usually mild and manageable with transient dose reduction or anti-diarrheic drugs.

Tocilizumab has been introduced in clinical practice after the publication of the phase III RCT (focuSSced trial[25]). The study population included dcSSc patients with a disease duration $\leq$ 5 years and with raised inflammatory serum markers (see **Table 1**).

The subcutaneous formulation (162 mg subcutenous weekly) was used in monotherapy. The primary study endpoint (change in the mRSS) was not met at 48 weeks, but the study showed preservation of pulmonary function in the tocilizumab group, whereas the placebo group showed a slight decrease. The cumulative distribution of change in %predicted FVC favored tocilizumab compared with placebo ($-$3.9 versus $-$0.6, $p = 0.0015$) and the mean difference in FVC change from baseline

Table 1
Characteristics of phase 3 studies

Trial Drug	Mechanism of Action	Inclusion Criteria	Treatment	IS	Endpoints	Duration	Results
Nintedanib (NTD) SENSCIS	Tyrosine kinase inhibition (FGF, VEGF, and PDGF)	*SSc-ILD* HRCT $\geq$10% Early ($\leq$7 years)	150 mg oral BID	Yes[a]	(1) Annual ΔFVC. (2) mRSS, SGRQ	52 weeks	↓ FVC decline in NTD ($p = 0.04$) No change in mRSS or SGRQ
Tocilizumab (TCZ) focuSSced	IL-6 receptor blockage	Early ($\leq$5 years) dcSSc (mRSS$\geq$10) Inflammation[b]	162 mg sc weekly	No	(1) mRSS. (2) Δ%pFVC	48 weeks	No significant mRSS change ($p = 0.098$) FVC change favored TCZ ($p = 0.0015$)

Abbreviations: %pFVC, % predicted forced vital capacity; BID, bis in die; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IS, immunosuppressive treatment; mRSS, modified Rodnan skin score; sc, subcutaneous; SGRQ, St. George's Respiratory Questionnaire; SSc, systemic sclerosis.

[a] Stable IS therapy for at least 6 months before study enrollment with prednisone $\leq$ 10 mg daily, methotrexate, or mycophenolate mofetil.

[b] At least one of the following: C-reactive protein $\geq$6 mg/L, ESR $\geq$28 mm/h, or platelet count $\geq 330 \times 10^9$/L.

was 167 mL in favor of tocilizumab. No significant increase in adverse events and serious adverse events was observed in the trial. Subsequent subanalyses[41] showed that SSc-ILD patients included in the trial and receiving tocilizumab had preservation of %predicted FVC over 48 weeks compared with placebo (−0.1% versus −6.3%) and this was particularly pronounced in patients with severe SSc-ILD patients as defined by lung involvement at HRCT >20% extent at baseline.

Other targeted treatments, including the anti-CD20 monoclonal antibody rituximab, have also been studied.[42] Unfortunately, the nature of the studies prevents drawing clear conclusions about its effectiveness and positioning for SSc-ILD, as most retrospective or uncontrolled prospective studies are so far available.[43–45] The results of the RECITAL study, a clinical trial comparing the efficacy of rituximab with CYC as first-line treatment in connective tissue disease (CTD)-related ILD have been recently published, with 40% of patients being represented by SSc-ILD cases. In this trial, Rituximab was not superior to CYC, as both drugs showed comparable improvement FVC% and patient-reported outcomes. Despite this, rituximab determined fewer side effects than CYC, as well as lower exposure to corticosteroids.[46] In this light, rituximab might be taken into consideration in specific populations, given the positive results observed in these studies, and it could also be considered in combination with nintedanib ± MMF.

Although the management of SSc-ILD patients has changed since the introduction of nintedanib and tocilizumab, many open questions on how to implement the full potential of these drugs are still unanswered. First, besides the many differences in the two study populations (including cutaneous subtype, enrichment in inflammatory patients, disease duration, see **Table 1**), the possibility of combining therapies—that is, with MMF, which is considered the "anchor drug" in SSc—was only allowed in the SENSCIS trial. This fundamental difference opens the possibility that the use of such a strategy even for tocilizumab might further increase the efficacy of the drug, as already observed for the nintedanib. This fascinating scenario should though be carefully investigated, given the possible synergistic effect in the beneficial side as well as in the rate and grade of adverse events. Moreover, even though the combination therapy of nintedanib plus MMF and/or methotrexate was allowed in the SENSCIS trial, other possible combinations have potential additional benefits, as recently reported in a multi-center real-life retrospective study of ninedanib in Italy.[47] Currently, while waiting for stronger prospective evidence, we advocate to start with immunomodulatory therapy in SSc patients with new onset or first detection ILD as these treatments have been shown to stabilize or even improve pulmonary function. The choice of drug, either MMF, TCZ, or their combination, should depend on a careful evaluation of extra-pulmonary manifestations (eg, skin, cardiac, and musculoskeletal involvement) and of specific disease features (eg, disease duration and elevation of inflammatory markers). In SSc-ILD patients with ongoing progression of ILD despite immunosuppressive treatment and in patients with rapidly declining FVC (>10% within 12 months) and >10% of ILD extent on HRCT additional treatment with nintedanib in combination with MMF could be considered.

Another matter of debate is whether a combination therapy should be advocated since the very beginning of SSc-ILD treatment, even in subclinical ILD (with the risk of potential adverse events in patients who may not progress) or whether an "add-on strategy" (ie, starting with MMF, then adding nintedanib) should be considered only for progressive patients (with the risk of irreversibly losing lung functionality). Both strategies might have pros and cons. In the first scenario, the need to wait for patients' lung deterioration and the occurrence of irreversible damage might be avoided. However, with the relatively low numbers of SSc-ILD patients that will

actually show progression, this scenario might also result in important overtreatment, urging the need to validate risk factors to accurately identify progressors.[38,48]

Following this line, a possible upfront combination therapy including nintedanib plus tocilizumab has been hypothesized by some authors as an alternative to HSCT, as it might offer the possibility of achieving beneficial effects on multiple domains including skin, musculoskeletal system and quality of life (QoL).[20,49] This is similar to what is currently recommended for SSc-PAH,[50] a field in which studies have identified combination therapies as the best therapeutic option, as they can significantly impact mortality and QoL.[51]

A clinical distinction should also be made for SSc-ILD patients with concomitant PH, who represent a group of patients at high risk of poor outcomes and who have been neglected or poorly represented in the studies published so far.[5,52] The possibility that these new treatments might be effective also in this subpopulation and that they could positively impact the evolution of PH is yet to be determined and offers exciting opportunities for the whole scleroderma community.

On this background, SSc-ILD experts have suggested that baseline HRCT-defined (sub)clinical ILD involvement[53] together with a complete evaluation of at-risk features for ILD progression should be taken into consideration to decide which is the most suitable strategy.[49] Despite this, it is crucial to remember that the best strategy should always meet patients' demands and preferences regarding the route of administration and the potential side effects should carefully be discussed, as they might limit patients' compliance.[54] Therefore, stratification for the occurrence of severe or intolerable side effects should also be implemented for a more comprehensive therapeutic algorithm.[55]

Follow-up Assessment

Despite the availability of therapeutic recommendations and additional options, we are currently lacking robust data-supported guidance for the specific follow-up of SSc-ILD patients, after therapy initiation. This reflects in different areas in the management of SSc-ILD cases, which require standardization and optimization.

Monitoring efficacy

Current data derived from RCTs and observational studies targeting SSc-ILD support the evaluation of treatment efficacy after average 12 months from drug initiation. Although this might follow regulatory requirements for the registration of drugs in the approved therapeutic armamentarium, this timespan may not represent the clinical approach of most physicians treating SSc-ILD.[48] As reported in a recent expert opinion article, patients may be assessed at least every 6 months with various tests which may capture different domains of SSc-ILD progression.[56] This timepoint, or even a shorter one, may reflect the need to verify the efficacy of the medication in stopping the progression and might be indirectly in line with the RCT data. In fact, protocols in which background medications were allowed at the beginning of the treatment phase, such as the case of methotrexate and mycophenolic acid in the SENSCIS trial,[24] required a stable medication status for at least six months. This reflects the fact that both tolerability and efficacy of the drugs might have reached a "steady state" after six months of administration and, therefore, start showing both beneficial effect and safety concerns. Moreover, data from both the SLS I, SLS II, SENSCIS, and FocuSSced have shown that curves presenting FVC decline over time show separation between placebo and treatment arms at 6 months.[16,18,24,25] In line with this, although one might feel urgency to evaluate 3 months after initiation of treatment, in particular in symptomatically progressive patients, the treating

physician should realize that the efficacy of available drugs mostly takes >3 months to become functionally and clinically apparent. In addition, the limited number of available drugs should be kept in mind when deciding that treatment is not efficacious.

Agreeing on 6-monthly evaluations, in particular after the initiation of new treatments, better guidance is desirable on which assessments should be performed, ideally reflecting a clinically meaningful improvement of SSc-ILD. The definition of "ILD progression" from Goh and colleagues[10] included FVC relative decline over 12 months ≥10% or FVC relative decline between 5-9% associated with a DLco relative decline≥15% and it was identified as a surrogate biomarker for mortality. Subsequently, a more heterogeneous definition of ILD progressive phenotype was used as inclusion criteria for the INBUILD study, considering various combinations of FVC, ILD extent, and symptoms worsening.[12] A joined initiative from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociaciòn Latinoamericana the Tòrax has recently released guidelines for the diagnosis and treatment of pulmonary progressive fibrosis (PPF) in fibrotic ILDs. These combine previous data from RCTs and observational studies and consider an ILD patient as PPF in case of at least 2 of worsening of respiratory symptoms, functional or radiological progression.[11] This more recent and multi-domain definition requires, therefore, multiple evaluations to be performed, and association with for example mortality, has not been fully addressed yet in SSc-ILD.

Pulmonary function testing. PFT is an effective follow-up assessment of SSc-ILD.[57] In particular, FVC represents the endorsed instrument for use in both RCTs and observational studies, contrary to DLco which was mostly used as a secondary outcome and not always showing positive results. Although DLco is less specific than FVC in identifying pure parenchymal disease changes and it is still part of both definitions of "ILD progression", it might reflect other concomitant changes such as anemia, vasculopathy, or emphysema. In this context, DLco decline in a patient with worsening respiratory symptoms but stable FVC/ILD extent on HRCT may guide the physician to investigate concomitant PH. Different definitions regarding progression based on PFT are available. In comparison to Goh and colleagues, Raghu and colleagues[11] have defined "functional progression" as FVC absolute decline ≥5% or DLco corrected absolute decline ≥10% over 12 months, the latter requiring a thorough exclusion of other possible causes. Both definitions have pros and cons: although only the former has been validated in SSc-ILD, the second ensures ILD is a relevant cause by the simultaneous presence of symptoms worsening or HRCT progression. Specific validation of the most recent functional definition of progression and comparison with the previous one in terms of prognostic impact in SSc-ILD is awaited.

High-resolution computed tomography. The extent of SSc-ILD on HRCT has been associated with both functional decline and mortality.[58] Nevertheless, only few studies showed numerical and probably not clinically meaningful changes in ILD extent detected on HRCT during treatment, although associated with functional changes.[25,38,59] In addition to identifying treatment effects, the increase of total ILD extent ≥ 2% over 12-24 months has been recently identified as an independent predictor of mortality, therefore representing another candidate surrogate biomarker. The recent guidelines include HRCT progression as one of the possible features of a PPF patient: in this context, not only the extent of ILD, but also the appearance of new ILD areas or transition from one ILD pattern to the other is considered ILD progression, despite no SSc-ILD specific data are available.[11] In addition, whether this evaluation may rely on visual or also on computerized quantitative evaluation is not yet

established. When moving from RCTs to clinical practice, the application of HRCTs in the follow-up of SSc-ILD patients is not standardized. A recent EUSTAR-SCTC survey has shown that almost one-third of the 205 responders regularly perform HRCTs in the follow-up of SSc-ILD cases, whereas the majority prescribe it only according to clinical judgment.[60] This included mostly cases with functional decline, new onset or worsening of dyspnea, or of crackles on auscultation. This is also in line with that derived from the European Consensus, in which there was disagreement on repeating HRCT annually after SSc-ILD diagnosis.[48] If applying the new definition of PPF, HRCT might be considered in all patients presenting functional decline or a worsening of respiratory symptoms. As for DLco, also HRCT is pivotal in the differential diagnosis of respiratory symptoms. Infections, thrombo-embolic events, and emphysema can be detected on HRCT and would then guide to a different therapeutic approach. These concomitant conditions might be missed if considering only functional tests during the follow-up evaluation. As this approach might lead to a high number of tests, algorithms suggesting when to scan the patients during the follow-up are eagerly awaited.

Other assessments. Additional evaluations, such as the 6-minute walking test and patients reported outcomes (including QoL and symptoms) also carry positive and negative aspects. When both have been used in RCT as secondary outcomes, no significant efficacy was detected for most of the evaluations performed.[61] This might reflect the multi-domain nature of these evaluations and the lack of specificity for SSc-ILD changes. Observational studies identified oxygen desaturation at the six minutes walking test, together with presence/history of arthritis, as a predictor for future functional worsening of SSc-ILD.[62] With a similar attitude, change in QoL or symptoms is something to always consider at a patient level, being the real target of the treatment. Lower performance in exercise test and increase in patients' complaints are indeed non-specific for SSc-ILD, but both should trigger further assessment to detect either ILD progression or concomitant extra-pulmonary complications.

Safety and additional considerations

Although SSc-ILD studies mostly target mortality or SSc-ILD progression, other events also represent important outcomes at patient level. The safety profile of the treatments is of pivotal importance, in particular for medications determining more stability than clinically meaningful improvement.[63] Although the adverse events profile of the medications is well known and strategies are available for the management of some of them (such as gastrointestinal and liver toxicities), the increased risk of infections using immunosuppressants remains a major concern. In this light, scientific societies' advice should be followed regarding vaccinations when using immunosuppressive agents.[64,65] In addition, guidance regarding prophylactic antibiotics to prevent opportunistic infections might be considered in the context of both ILD and immunosuppression.

The overall follow-up assessment of a patient with SSc-ILD should go beyond the control of lung functionality and drug toxicities: it should consider a multidisciplinary team evaluation, in collaboration with other specialists, including pulmonologists and radiologists.[27] Both specialists are pivotal in the close collaboration with the rheumatologists, to identify clinically meaningful progression, rule out other causes for the clinical worsening of a patient, and to choose the optimal drug strategy. Bronchoalveolar lavage, for example, represents a useful instrument to rule out infections and other concomitant lung pathologies, requiring pulmonologist experience and expertise.

Evidence regarding the additional beneficial effect of non-pharmacological interventions is scarce. These include pulmonary rehabilitation, as a very safe procedure

Box 1
Research agenda regarding the treatment of SSc-ILD

Initiation: when to start treatment?

To treat at diagnosis (primary prevention of progression) versus at progression (secondary prevention), identifying high-risk patient profiles.

Combination: is an upfront combination superior to an add-on treatment strategy?

Upfront versus sequential use of immunosuppressants and/or antifibrotics, taking also into account extra-pulmonary disease features.

Supportive measures: which supportive measurements are most effective for patient's symptoms?

Identify interventions most effective on patients' perception, such as dyspnea, QoL, cough, fatigue, depression, also including medications indirectly targeting ILD.

Continuation: how long should SSc-ILD treatment be continued?

Lack of data on long-term efficacy and treatment tapering/withdrawal.

Monitoring: how often and according to which definition should we evaluate the efficacy of initiated treatment?

Validation of SSc-ILD multi-domain definition of progression, and timing of assessments.

to expose SSc-ILD patients to,[66] as well as oxygen supplementation. The latter is mostly seen as a treatment failure outcome and usually started when hypoxia presents at rest. In reality, SSc-ILD patients might present with desaturation and hypoxia during exercise while not being hypoxic at rest. A recent prospective RCT administered oxygen supplementation to patients with ILD secondary to different causes and hypoxemia after the 6MWT showed a beneficial effect on QoL and dyspnea.[67] In this light, oxygen supplementation could be offered earlier to SSc-ILD patients, to preserve QoL. Finally, referral to lung transplantation should be considered when the situation is deteriorating despite maximum pharmacological and non-pharmacological efforts. Although the possible simultaneous involvement of the cardiac and gastrointestinal systems has been regarded as a possible contraindication, more recent data showed comparable outcomes in SSc-ILD patients after lung transplantation as compared with other transplanted patients, despite the high prevalence of severe esophageal dysfunction in this group.[26]

SUMMARY

The body of evidence on how to treat SSc-ILD is definitely growing. However, several major knowledge gaps have been identified.[68] In our opinion, future research should focus on the practical use of the available drugs to answer specific unmet needs in the therapeutic approach. This would allow us to move beyond expert opinions and compensate for the lack of real evidence on different points with specific strategies, including initiation, combination, and continuation of treatment and monitoring (**Box 1**).

CLINICS CARE POINTS

- Interstitial lung disease (ILD) is highly prevalent in systemic sclerosis (SSc) and associated with high mortality
- All SSc patients need to be screened for ILD with high-resolution computed tomography

- SSc-ILD course is highly variable, and prediction at the individual patient level is challenging
- Next to cyclophosphamide, mycophenolate mofetil and hematopoietic stem cell transplantation, nintedanib, and tocilizumab have proven efficacy in the treatment of SSc-ILD
- Different profiles of concomitant medications and patients' characteristics make the efficacy data of randomized controlled trials not directly comparable.
- Follow-up evaluation of SSc-ILD may include a combination of functional, radiologic, and clinical assessment, to identify progressive patients.
- Timing and indication of the specific assessment parameters for follow-up of SSc-ILD are not clearly indicated.

DISCLOSURE

C. Bruni received consulting fees and/or honoraria from Actelion, Eli-Lilly, Boehringer Ingelheim. Research grants from Foundation for research in Rheumatology (FOREUM), Gruppo Italiano Lotta alla Sclerodermia (GILS), European Scleroderma Trials and Research Group (EUSTAR), Scleroderma Clinical Trials Consortium (SCTC). Educational grants from AbbVie. C. Campochiaro, received consulting fees and/or honoraria from SOBI, Novartis, Pfizer, Roche, Jannsen Boehringer Ingelheim. J.K. de Vries-Bouwstra, received consulting fees from Abbvie, Janssen and Boehringer Ingelheim, and received research grants from Roche, Galapagos, Janssen, ReumaNederland, NVLE (Dutch society for patients with lupus, scleroderma, MCTD and APS).

REFERENCES

1. Hoffmann-Vold AM, Fretheim H, Halse AK, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. Am J Respir Crit Care Med 2019;200(10):1258–66.
2. Vonk MC, Broers B, Heijdra YF, et al. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. Ann Rheum Dis 2009;68(6):961–5.
3. Walker UA, Tyndall A, Czirjak L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66(6):754–63.
4. Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76(11):1897–905.
5. Young A, Vummidi D, Visovatti S, et al. Prevalence, treatment, and outcomes of coexistent pulmonary hypertension and interstitial lung disease in systemic sclerosis. Arthritis Rheumatol 2019;71(8):1339–49.
6. Rubio-Rivas M, Royo C, Simeon CP, et al. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum 2014;44(2):208–19.
7. Elicker BM, Kallianos KG, Henry TS. The role of high-resolution computed tomography in the follow-up of diffuse lung disease: Number 2 in the Series "Radiology" Edited by Nicola Sverzellati and Sujal Desai. Eur Respir Rev 2017;26(144). https://doi.org/10.1183/16000617.0008-2017.
8. Suliman YA, Dobrota R, Huscher D, et al. Brief report: pulmonary function tests: high rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. Arthritis Rheumatol 2015;67(12):3256–61.

9. Hoffmann-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis 2021;80(2):219–27.
10. Goh NS, Hoyles RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol 2017;69(8):1670–8.
11. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2022;205(9):e18–47.
12. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. Eur Respir J 2022;59(3). https://doi.org/10.1183/13993003.04538-2020.
13. Ruaro B, Confalonieri M, Matucci-Cerinic M, et al. The treatment of lung involvement in systemic sclerosis. Pharmaceuticals 2021;14(2). https://doi.org/10.3390/ph14020154.
14. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76(8):1327–39.
15. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54(12):3962–70.
16. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354(25):2655–66.
17. Bruni C, Tashkin DP, Steen V, et al. Intravenous versus oral cyclophosphamide for lung and/or skin fibrosis in systemic sclerosis: an indirect comparison from EUSTAR and randomised controlled trials. Clin Exp Rheumatol 2020;38(Suppl 125 3):161–8.
18. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4(9):708–19.
19. Volkmann ER, Tashkin DP, Li N, et al. Mycophenolate mofetil versus placebo for systemic sclerosis-related interstitial lung disease: an analysis of scleroderma lung studies I and II. Arthritis Rheumatol 2017;69(7):1451–60.
20. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. N Engl J Med 2018;378(1):35–47.
21. Burt RK, Shah SJ, Dill K, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet 2011;378(9790):498–506.
22. van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA 2014;311(24):2490–8.
23. Ciaffi J, van Leeuwen NM, Boonstra M, et al. Evolution of systemic sclerosis-associated interstitial lung disease one year after hematopoietic stem cell transplantation or cyclophosphamide. Arthritis Care Res 2022;74(3):433–41.
24. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380(26):2518–28.

25. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2020;8(10):963–74.
26. Miele CH, Schwab K, Saggar R, et al. Lung transplant outcomes in systemic sclerosis with significant esophageal dysfunction. A comprehensive single-center experience. Ann Am Thorac Soc 2016;13(6):793–802.
27. Farina N, Benanti G, De Luca G, et al. The role of the multidisciplinary health care team in the management of patients with systemic sclerosis. J Multidiscip Healthc 2022;15:815–24.
28. Assassi S, Sharif R, Lasky RE, et al. Predictors of interstitial lung disease in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. Arthritis Res Ther 2010;12(5):R166.
29. Becker M, Graf N, Sauter R, et al. Predictors of disease worsening defined by progression of organ damage in diffuse systemic sclerosis: a European Scleroderma Trials and Research (EUSTAR) analysis. Ann Rheum Dis 2019;78(9):1242–8.
30. Hoffmann-Vold AM, Aalokken TM, Lund MB, et al. Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. Arthritis Rheumatol 2015;67(8):2205–12.
31. Khanna D, Tashkin DP, Denton CP, et al. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. Am J Respir Crit Care Med 2020;201(6):650–60.
32. Nihtyanova SI, Denton CP. Scleroderma lung involvement, autoantibodies, and outcome prediction: the confounding effect of time. J Rheumatol 2017;44(4):404–6.
33. Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66(6):1625–35.
34. Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. Nat Rev Dis Prim 2015;1:15002.
35. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390(10103):1685–99.
36. McNearney TA, Reveille JD, Fischbach M, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum 2007;57(2):318–26.
37. Hudson M, Pope J, Mahler M, et al. Clinical significance of antibodies to Ro52/TRIM21 in systemic sclerosis. Arthritis Res Ther 2012;14(2):R50.
38. Distler O, Assassi S, Cottin V, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. Eur Respir J 2020;55(5). https://doi.org/10.1183/13993003.02026-2019.
39. Huang J, Maier C, Zhang Y, et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. Ann Rheum Dis 2017;76(11):1941–8.
40. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22):2071–82.
41. Roofeh D, Lin CJF, Goldin J, et al. Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol 2021;73(7):1301–10.
42. Campochiaro C, Allanore Y. An update on targeted therapies in systemic sclerosis based on a systematic review from the last 3 years. Arthritis Res Ther 2021;23(1):155.

43. Goswami RP, Ray A, Chatterjee M, et al. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. Rheumatology 2021;60(2):557–67.
44. Campochiaro C, De Luca G, Lazzaroni MG, et al. Safety and efficacy of rituximab biosimilar (CT-P10) in systemic sclerosis: an Italian multicentre study. Rheumatology 2020;59(12):3731–6.
45. Elhai M, Boubaya M, Distler O, et al. Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. Ann Rheum Dis 2019;78(7):979–87.
46. Maher TM, Tudor VA, Saunders P, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med 2023;11(1):45–54.
47. Campochiaro C, De Luca G, Lazzaroni MG, et al. POS0890 nintedanib real-life efficacy and safety in systemic sclerosis (SSc)-intertistial lung disease (ILD): an italian multicentre preliminary study. Ann Rheum Dis 2022;81(Suppl 1):741–2.
48. Hoffmann-Vold AM, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatology 2020;2(2):E71–83.
49. Khanna D, Denton CP. Integrating new therapies for systemic sclerosis-associated lung fibrosis in clinical practice. Lancet Respir Med. Jun 2021;9(6):560–2.
50. Hassoun PM, Zamanian RT, Damico R, et al. Ambrisentan and tadalafil up-front combination therapy in scleroderma-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2015;192(9):1102–10.
51. Coghlan JG, Galie N, Barbera JA, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. Ann Rheum Dis 2017;76(7):1219–27.
52. Bruni C, Guignabert C, Manetti M, et al. The multifaceted problem of pulmonary arterial hypertension in systemic sclerosis. The Lancet Rheumatology 2021;3(2):e149–59.
53. Roofeh D, Jaafar S, Vummidi D, et al. Management of systemic sclerosis-associated interstitial lung disease. Curr Opin Rheumatol 2019;31(3):241–9.
54. El Aoufy K, Bruni C, Rasero L, et al. Patient preferences for systemic sclerosis treatment: a descriptive study within an Italian cohort. J Scleroderma Relat Disord 2021;6(2):165–9.
55. Bruni C, Heidenreich S, Duenas A, et al. Patient preferences for the treatment of systemic sclerosis-associated interstitial lung disease: a discrete choice experiment. Rheumatology 2022. https://doi.org/10.1093/rheumatology/keac126.
56. Khanna D, Lescoat A, Roofeh D, et al. Systemic sclerosis-associated interstitial lung disease: how to incorporate two food and drug administration-approved therapies in clinical practice. Arthritis Rheumatol 2022;74(1):13–27.
57. Roofeh D, Barratt SL, Wells AU, et al. Outcome measurement instrument selection for lung physiology in systemic sclerosis associated interstitial lung disease: A systematic review using the OMERACT filter 2.1 process. Semin Arthritis Rheum 2021;51(6):1331–41.
58. Landini N, Orlandi M, Bruni C, et al. Computed tomography predictors of mortality or disease progression in systemic sclerosis-interstitial lung disease: a systematic review. Front Med 2021;8:807982.

59. Goldin J, Elashoff R, Kim HJ, et al. Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study. Chest 2009;136(5):1333–40.
60. Bruni C, Chung L, Hoffmann-Vold AM, et al. High-resolution computed tomography of the chest for the screening, re-screening and follow-up of systemic sclerosis-associated interstitial lung disease: a EUSTAR-SCTC survey. Clin Exp Rheumatol 2022. https://doi.org/10.55563/clinexprheumatol/7ry6zz.
61. Hoffmann-Vold AM, Allanore Y, Bendstrup E, et al. The need for a holistic approach for SSc-ILD - achievements and ambiguity in a devastating disease. Respir Res 2020;21(1):197.
62. Wu W, Jordan S, Becker MO, et al. Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. Ann Rheum Dis 2018;77(9):1326–32.
63. Kafaja S, Clements PJ, Wilhalme H, et al. Reliability and minimal clinically important differences of forced vital capacity: results from the Scleroderma Lung Studies (SLS-I and SLS-II). Am J Respir Crit Care Med 2018;197(5):644–52.
64. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79(1):39–52.
65. Curtis JR, Johnson SR, Anthony DD, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 4. Arthritis Rheumatol 2022;74(5):e21–36.
66. Liem SIE, Vliet Vlieland TPM, Schoones JW, et al. The effect and safety of exercise therapy in patients with systemic sclerosis: a systematic review. Rheumatol Adv Pract 2019;3(2):rkz044.
67. Visca D, Mori L, Tsipouri V, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. Lancet Respir Med 2018;6(10):759–70.
68. Campochiaro C, Lazzaroni MG, Bruni C, et al. Open questions on the management of targeted therapies for the treatment of systemic sclerosis-interstitial lung disease: results of a EUSTAR survey based on a systemic literature review. Ther Adv Musculoskelet Dis 2022;14. 1759720X221116408.