# Systemic sclerosis associated interstitial lung disease: a survey of current practices in France.

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# Systemic sclerosis associated interstitial lung disease: a survey of current practices in France

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***Abstract***

**Background:** Interstitial lung disease (ILD) is the leading cause of mortality in systemic sclerosis (SSc).

**Objective:** We performed an overview of the diagnostic approaches, follow-up and treatment strategies used in France for the management of SSc-associated ILD (SSc-ILD).

**Design:** Structured nationwide online survey.

**Methods:** A structured nationwide online survey was submitted to participants *via* the French Medical Societies for Internal Medicine and Pneumology, and research groups on SSc-ILD from May 2018 to June 2020. The 79 multiple-choice and 9 open-ended questions covered the screening of ILD at baseline, monitoring of patients with established SSc-ILD and its management. Fourteen optional vignettes exploring different clinical phenotypes of SSc-ILD were submitted to evaluate therapeutic decisions.

**Results:** All of the 93 participants screened SSc patients for ILD at baseline with 83 (89%) participants relying on a systematic chest computed tomography (CT) scan. Pulmonary function tests (PFT) were prescribed by 87 (94%) participants at baseline and during follow-up. Treatment was started based on abnormal PFT (95%), chest CT scan characteristics (89%), worsening dyspnoea (72%) and drop in $SpO_2$ during 6-min walk tests (66%). First-line therapy was cyclophosphamide (CYC) (89%), mycophenolate mofetil (MMF) (83%) and prednisone (73%). Rituximab as second-line immunosuppressive therapy (41%) was preferred to antifibrotic agents (18%), and a median daily prednisone dose of 10 mg (interquartile range, 10–15) was prescribed by 73% participants. Extensive SSc-ILD with worsening PFT (95%), regardless of diffusing capacity for carbon monoxide values and skin extension, were more likely to be treated, and CYC was favoured over MMF ($p < 0.01$). Extensive SSc-ILD with disease duration of less than 5 years was also a criterium for treatment initiation.

**Conclusion:** This overview of practices in diagnosis, follow-up and treatment of SSc-ILD in France describes real-life management of patients. It highlights heterogeneity in this management and gaps in current strategies that should be addressed to improve and harmonize clinical practices in SSc-ILD.

***Keywords:*** diagnostic management, interstitial lung disease, systemic sclerosis, therapeutic management

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## Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by autoimmunity, microvascular injury and tissue fibrosis.[1] Its incidence is approximately 10–20 patients per 1 million inhabitants per year and middle-age women are mostly affected with a sex ratio of 7 to 1.[2] Interstitial lung disease (ILD) is the leading cause of death in SSc,

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closely followed by pulmonary arterial hypertension (PAH).[3–6] Diagnosis of SSc-associated ILD (SSc-ILD) is usually based on a multimodal approach combining clinical aspects, high-resolution computed tomography (HRCT), and pulmonary function tests (PFT).[3,7,8] There is no consensual approach to assessing SSc-ILD progression,[8] although a recent European initiative sought to identify commonly accepted risk factors and clinical guidelines.[9] The extent of lung involvement on HRCT at baseline, combined with reduced or declining forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), is predictive of mortality.[10,11] Other risk factors for the development or progression of SSc-ILD include diffuse cutaneous SSc (dcSSc), anti-topoisomerase 1 antibodies, African American ethnicity and older age at disease onset.[12,13] For patients with limited SSc-ILD, Wu *et al.*[14] suggested that $SpO_2 \leqslant 94\%$ after 6-min walk test (6MWT) and a history of arthritis were independent predictors for ILD progression.

Therapeutic approaches vary from watchful waiting and close monitoring in the early stages of the disease to immunosuppression and rapid treatment escalation in the case of progressive or severe ILD aiming to stabilize the disease.[15–20]

The landscape of treatment armamentarium is also rapidly evolving with the recent approval of nintedanib and tocilizumab, whose exact place remains to be clarified.

Management of SSc-ILD is challenging, and current guidelines have had to strike a balance between disease-assessment and the lack of effective treatment options. Therefore, little is known on how this translates into medical practice. We sought to get an overview of the diagnostic approach, follow-up and treatment strategies commonly used in France *via* a nationwide survey, which was performed before the approval of nintedanib and tocilizumab.

## Methods

### *Online survey of French specialists*

We developed a structured online survey (Supplementary Data, S1) to collect data on patient management by physicians treating SSc-ILD. Emails containing a link to the online survey were sent to physicians in May 2018, and all answers were considered up to June 2020, through the national French Medical Societies of Internal Medicine and Pneumology, with the support of the OrphaLung network for rare pulmonary diseases and the French Research Group on Systemic Sclerosis (GFRS). The survey was also open to any other medical specialty managing SSc on a regular basis. Eligible participants were required to be practicing physicians caring for patients with SSc-ILD. Minimum experience in the field of SSc was not required.

The survey was conducted in French (its English translation can be found in Supplementary Data Section, S1). It comprised 79 defined-choice and 9 open-ended questions, related to the following topics: demographics, management of ILD screening at the diagnosis of SSc, monitoring of patients with established SSc-ILD, and therapeutic management of SSc-ILD. Reporting of the research survey complied with the checklist from guidelines provided by Kelley *et al.*[21] (Supplementary Data, S2).

At the onset of the survey, prospective participants were informed about the content and purpose of the survey. Survey participants did not receive any payment but were given the incentive to appear as collaborators of the project. Incomplete or redundant submissions by the same participant were not analysed.

### *Clinical vignettes*

In addition to the practice survey, a set of 14 optional clinical vignettes was submitted to the participants. Each vignette explored a specific phenotype of SSc-ILD in relation to its progression over time (Supplementary Data, Table S3). The vignettes were constructed to assess how decision-making would be influenced by the following clinical, radiological and functional features: (1) skin involvement, (2) time from disease onset, (3) presence or absence of PAH, (4) extensive or limited ILD and (5) PFT parameters. We empirically chose FVC cutoff values of 88%pred. and 66%pred. to illustrate the extent of 'lung restriction'; similarly, DLCO cutoffs of 80%pred., 49%pred. and 32%pred. were chosen to reflect the extent of pulmonary gas exchange deterioration. Based on these criteria, participants had to decide, depending on the scenario, if they would initiate a specific treatment in each situation, and which first-line therapy they would choose.

### *Statistics*

Continuous variables are expressed as median values with their interquartile range (IQR). Extreme values are specified when necessary. Categorical variables are expressed as number and percentage of respondents. Categorical variables were compared using a chi$^2$ test or a Fisher's exact test when appropriate. For the analysis of the clinical vignettes, we used the McNemar test to assess the concordance level between the choices of treatment between two different clinical situations. All tests were two-sided. A $p$ value $< 0.05$ was considered statistically significant; 95% confidence intervals (95% CI) are specified. Statistical analyses were performed using GraphPad Prism Software version 7.0 (GraphPad Software, 2016), R statistical software, version 4.0.4. and Microsoft Office Excel 2016.

## Results

### *Survey response and participant characteristics*

Answers were collected from May 2018 to June 2020. The survey was completed 100 times. Among the respondents, seven physicians had answers that appeared twice, and, therefore, their second participation was disregarded.

Participant characteristics and features of patient recruitment within associated healthcare institutions are summarized in Table 1. All but 1 participant were hospitalists, with 18 Full Professors and 9 Associate Professors among the respondents. Fourteen residents also took part. Seventy-two of 93 participants were specialists in clinical immunology ('Médecine Interne et Immunologie Clinique') and 18 of 93 were specialists in respiratory medicine. Only three rheumatologists took part in the study and were not considered in the analysis for comparisons of attitudes between the different specialists.

### *Diagnostic work-up of SSc in a patient with ILD*

For recently diagnosed ILD suggestive of pulmonary involvement of SSc, most participants (77%) refer to classification criteria of SSc. Seventy-one (76%) respondents use the ACR/EULAR criteria with only 8 (9%) preferring the VEDOSS approach.[22] Twenty-one (23%) participants systematically discuss SSc-ILD diagnosis at multidisciplinary team (MDT) ILD meetings; 47 (51%) do so on occasion, and 12 (13%) rarely do so. Thirty-three (35%) participants discuss their newly diagnosed patients during routine specialty group meetings, while 11 (12%) state that they do not have a MDT approach at their local institution. Among the 46 (49%) participants who have specialized SSc MDT meetings, 3 always discuss the diagnoses, 23 sometimes and 10 do so exceptionally – while 10 never do so. The following procedures are performed for an early diagnosis of ILD and/or SSc: specific antibodies for SSc (92%), cardiac biomarkers (88%), 'protocolised blood tests' (72%), idiopathic inflammatory myositis autoantibody assays (44%) and microbiological studies (23%). Nearly all participants (98%) require transthoracic echocardiography to be systematically performed at baseline. Occupational exposure surveys are conducted by 43 (46%) participants.

### *ILD screening in a newly diagnosed SSc*

All participants screen newly diagnosed SSc patients for ILD. Eighty-three (89%) participants rely on a systematic chest computed tomography (CT) scan. A chest X-ray is performed by 40 (43%) participants, whereas 26 (28%) state that it is unnecessary. Eighty-seven (94%) systematically prescribe PFT. A 6MWT is performed at baseline by 65% of participants. Systematic ABG are required by 28 (30%) participants, whereas 14 (15%) find them unnecessary at the time of SSc diagnosis. Diagnostic approaches for ILD screening do not significantly differ between medical specialities, apart from systematic ABG, more frequently performed by clinical immunologists than by respiratory specialists ($p = 0.034$) (Supplementary Data, Table S4). Similarly, respiratory specialists are more likely to prescribe cardiopulmonary exercise testing (CPET).

Self-reported experience in the management of SSc did not significantly impact decisions although only one in three of the least experienced physicians prescribe chest CT scans on diagnosis (Supplementary Data, Table S5). More experienced physicians (>11 years practice) tended to prescribe fewer 6MWT on screening.

### *Follow-up in SSc patients without overt ILD*

PFT are prescribed by 94% of respondents in the longitudinal follow-up of SSc patients without overt baseline ILD. Chest CT scans are

**Table 1.** Characteristics of participants and their associated healthcare institutions.

| Characteristics of the participants | *n* |
|---|---|
| Experience in SSc management | |
| Participants with no experience in SSc | 3 |
| Participants with less than 1 year of experience in SSc | 10 |
| Participants with 1–3 years of experience in SSc | 20 |
| Participants with 3–10 years of experience in SSc | 31 |
| Participants with more than 10 years of experience in SSc | 29 |
| Experience in ILD management | |
| No experience in ILD | 1 |
| Experience in CTD-associated ILD | 6 |
| Experience of less than 1 year in ILD | 8 |
| Experience of 1–3 years in ILD | 15 |
| Experience of 3–10 years in ILD | 35 |
| Experience of more than 10 years | 28 |
| Associated healthcare institutions | |
| Number of associated institutions | 46 |
| Estimated number of SSc patients per participant | |
| ⩽5 patients | 4 |
| 6–9 patients | 6 |
| 10–30 patients | 18 |
| 31–50 patients | 17 |
| 51–99 patients | 16 |
| ⩾100 patients | 32 |
| Estimated proportion of SSc-ILD per participant | |
| Not known | 34 |
| 40% | 8 |
| 30% | 12 |
| 20% | 12 |
| 10% | 9 |

ILD, interstitial lung disease.

performed by 37% of participants, and chest X-rays by 35%. ABG are prescribed by 15%. PFT are more likely to be performed in the case of clinical deterioration (80%) or worsening of CT scan images (75%). Participants are also more likely to perform PFT on patients with dcSSc (35%) rather than limited cutaneous SSc (lcSSc) (17%), and if there is evidence of progressive ILD within 5 years from baseline. Intervals between consecutive follow-up PFT are 12 months in 62% of participants followed by 6 month (25%) and 3 months (3%). Conversely, systematic chest CT scans are only occasionally prescribed (12%). dcSSc lead to more CT scans being prescribed than lcSSc (33% *versus* 6%).

### *Follow-up in proven SSc-ILD*

Systematic PFT are prescribed by 97% of participants for the follow-up of SSc-ILD. Less than half (47%) performs them annually, whereas 39% schedule PFT every 6 months, or every 3 months (4%). Systematic chest X-rays seem to be preferred to chest CT scans (57% *versus* 31%). Sixty-four (69%) participants state that they do not prescribe systematic chest CT scans once SSc-ILD has been diagnosed and only do so when they suspect clinical (98%) or functional deterioration (66%). Other indications for chest CT scans, as stated by participants, are (1) dcSSc patients with a time from disease onset of less than 5 years (33%), and (2) lcSSc patients with disease progression of less than 5 years (14%). Echocardiography is systematically prescribed (95%) and reiterated on an annual (90%) or semi-annual basis (8%).

### *Interpretation of functional and imaging studies*

*PFT: cutoff values.* Spirometry with DLCO is prescribed systematically by 89 (96%) and 87 (94%) participants. Only 63 (68%) have total lung capacity (TLC) measurements performed. The median cutoff value for DLCO is 70%pred. (IQR, 70–75) under which ILD is suspected. Similarly, the carbon monoxide transfer coefficient (KCO) is considered abnormal for values under 70%pred. (IQR, 70–75). The median threshold value for FVC that is used for estimating restrictive ventilatory defect is 80%pred. (IQR, 70–80). Threshold values for FVC, DLCO and KCO chosen by clinical immunologists are

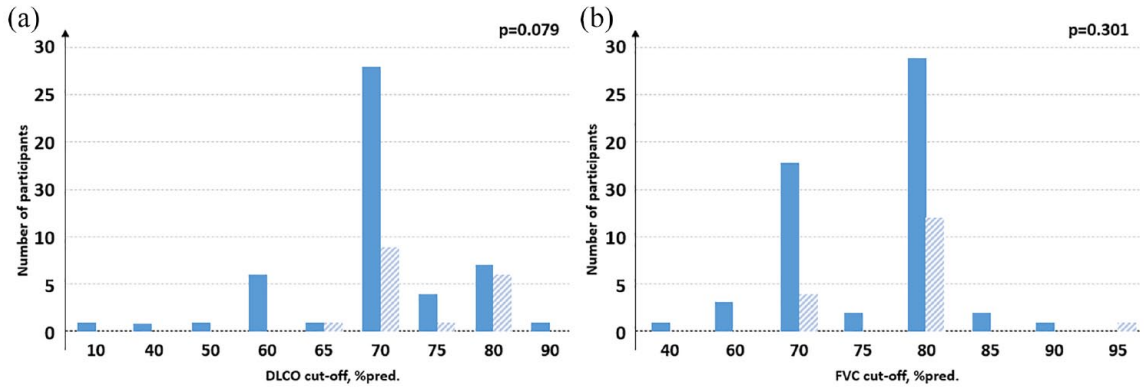


**Figure 1.** Cutoff values for (a) DLCO and for (b) FVC, below which pulmonary function tests are considered as abnormal.
Values are presented according to the speciality of the participants: clinical immunology ( ) and pneumology ( ).

lower than those defined by pulmonologists. The latter choose higher cutoff values to define abnormal PFT but ranges are smaller (Figure 1). Difference in duration of SSc management did not impact the chosen threshold values between participants.

*Procedures for chest CT scans.* An injected contrast agent is prescribed for chest CT scans on a systematic basis by 10 (11%) participants (Figure 2). Reasons for ordering contrast CT scans (by 36 participants) are presented in Figure 2. Most participants rely on the radiologist's judgement when opting for prone CT lung imaging (Figure 2).

*Chest CT scan: grading ILD.* Visual fibrotic scoring is the preferred method for grading the extent of ILD with 24 (26%) participants using the stepwise approach by Goh *et al.*[23] criteria, while only 6 (6%) use the Wells' criteria.[24] Six (6%) participants claim to use computer-aided assessment tools and only 2 assess ILD on CT scans without input from radiologists.

### *Key features for decision-making*

In descending order of frequency, key features for implementing treatment for SSc-ILD are abnormal PFT (95%), chest CT scan features (89%), worsening dyspnoea (72%), drop in $SpO_2$ during 6MWT (66%), associated PAH (48%), '6MWT results' (45%), ABG findings (45%) and low partial pressure of oxygen (24%). Answers do not significantly differ between pulmonologists and clinical immunologists.

Among PFT parameters, a 15% deterioration of DLCO values over a 12-month period is considered to be the most frequently used parameter for initiating treatments (71%), followed by a 10% deterioration of FVC values over a 12-month period (62%), a static infra-threshold value of DLCO (58%), a static infra-threshold value of FVC (46%), a 10% drop in FVC from diagnosis (27%), a 10% drop in TLC over a 12-month period (25%), an abnormal TLC (19%), and finally, a 10% drop in TLC from diagnosis (17%).

Radiological criteria cited by participants for initiating treatment are the extensive nature of the ILD (83%), the increase in ground-glass opacities (51%), and a predominance of honeycombing (6%).

When combining functional and radiological features, those that are the most frequently used in the therapeutic decision-making processes are (1) extensive ILD on CT scan (70%), (2) a 15% deterioration of DLCO values over a 12-month period (65%), (3) worsening dyspnoea (57%), (4) a 10% deterioration of FVC values over a 12-month period (57%) and (5) desaturation during a 6MWT (40%).

When asked to sort by importance the hereinabove criteria, 53 (57%) participants rank dyspnoea as the primary reason for initiating treatment.

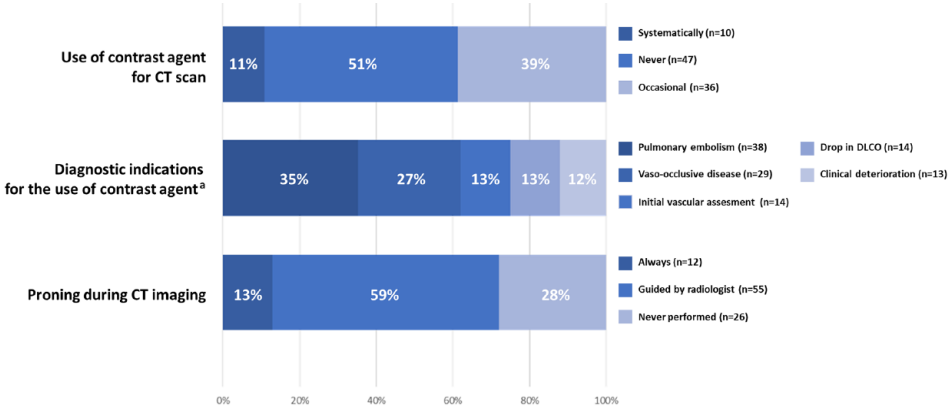


**Figure 2.** Interpretation of functional and imaging studies.
[a]Percentages calculated from the overall answers (n = 108) from a multiple-choice question, as provided by 36 participants who order contrast CT scans based on clinical contexts.

The aggravation of DLCO and FVC are thereafter mentioned. Extensive ILD shown on CT scans is only used as a treatment-initiating factor after the patient's functional abilities have been assessed.

### *Therapeutic approaches*

*Immunosuppressive and associated treatment strategies.* When initiating treatment, 76 (82%) participants systematically discuss their choices during MDT or routine specialty group meetings, regardless of their speciality (i.e. pulmonology or clinical immunology).

First-line therapies for the treatment of SSc-ILD are cyclophosphamide (CYC) (89%), mycophenolate mofetil (MMF) (83%), prednisone (73%), azathioprine (AZA) (20%), rituximab (18%), anti-fibrotic treatment (14%), methotrexate (MTX) (9%), ilomedine (2%), bosentan (2%), and sildenafil (2%). Autologous stem cell transplantation (ASCT) is mentioned by 17 of 93 (18%) participants as a potential first-line strategy and 23% intend to enrol their patients in therapeutic trials (23%) from the time of diagnosis. Sixty-three (68%) participants have a preferred first-line therapy: MMF ($n = 20$), CYC ($n = 20$), prednisone ($n = 13$), MMF and prednisone ($n = 4$), CYC and prednisone ($n = 2$) and ASCT ($n = 2$). Choices of preferred first-line therapies according to medical speciality and experience in SSc management are presented in Tables S6 and S7 (Supplementary Data).

Rituximab is the preferred second-line therapy ($n = 38$, 41%), followed by CYC (33%), MMF (33%) and AZA (22%). ASCT, antifibrotic therapy and therapeutic trial are similarly suggested (20, 18% and 17%, respectively). Other therapeutic options are referred to by less than 5% of respondents (i.e. MTX, mTOR inhibitors, calcineurin inhibitors, iloprost, bosentan, sildenafil, tocilizumab and abatacept). Participants once again cite rituximab as their first choice for a third-line treatment (33%). ASCT is considered by a quarter of participants and is a preferred third-line option among alternatives such as MMF (19%), an antifibrotic (19%) and CYC (16%). Organ transplantation is cited by two participants as a potential third-line therapy.

Treatment duration for CYC ranges from 3 months (4%) to 12 months (19%), with most respondents (76%) prescribing an initial therapy for a 6-month period.

All but eight participants systematically use steroids for SSc-ILD. Steroid dosing ranges from 5 mg (3%) to $\geqslant$ 20 mg (6%) q.d. with a preference for 10 mg q.d. (41%) and 15 mg q.d. (27%).

Eighteen (19%) participants have prescribed nintedanib, and 9 (10%) pirfenidone for SSc-ILD patients. Three (3%) participants believe SSc to be a contraindication for pulmonary transplantation, whereas 25 (27%) participants have patients who have been transplanted. Eighteen (19%) participants have managed patients who have had ASCT.

When asked to rate the expected efficacy of treatments for SSc-ILD on a scale of 0 (no efficacy) to 4 (excellent), participants provided an average

score of 1.8 (95%CI, 1.7-1.9), with a maximum score of 3.

*Proton-pump inhibitors (PPI).* PPI prescription in SSc-ILD is systematic for 43 (46%) participants. They are given for clinical symptoms of gastro-esophageal reflux disease (GERD) by 46 (49%), whereas a minority (4%) prescribes PPI only for proven GERD.

*Differences in approaches according to medical speciality.* Therapeutic approaches are compared based on the medical speciality of the participants and do not differ significantly except for the use of antifibrotic agents and enrolment in therapeutic trials which are more often reported by pulmonologists ($p = 0.016$ and 0.027, respectively). Pulmonologists tend to prescribe more steroids, although this attitude does not differ significantly from that of clinical immunologists. Furthermore, steroid dosing is similar in both groups. There is also no difference for the prescription of CYC and MMF as first-line therapies.

### *Clinical vignettes*

Sixty-eight (73%) participants answered the clinical vignettes, including 13 pulmonologists and 3 rheumatologists. Treatments are least prescribed for scenarios 1 and 8, which depict SSc with limited ILD and normal PFT, with respectively 72% and 82% of participants deciding not to treat SSc-ILD. When steroids are used, they are not initiated for ILD but for the disease 'as a whole' or for extra-respiratory features – as stated by more than half of the participants (55% for vignette 1 and 50% for vignette 2).

Conversely, nearly all participants introduce treatment for ILD for extensive forms with worsening PFT over a 6-month period (i.e. vignettes 6, 7, 13 and 14). Steroids, in such circumstances, are never used alone and are associated by more than 80% of participants with an immunosuppressor, usually CYC and to a lesser extent MMF (Figure 3(a)). CYC seems to be preferred by participants for patients with extensive ILD with worsening PFT, regardless of time from onset, DLCO or FVC values (Figure 3(a)).

The decision to initiate treatment may be influenced by the time from disease onset (Figure 3(b)). Participants are more likely to introduce therapy for SSc patients with extensive ILD with a time from disease onset of less than 5 years.

Borderline DLCO values, on the other hand, rarely influence decision-making for treatment initiation (Figure 3(c)). Lower DLCO values only lead to treatment initiation in scleroderma patients with extensive ILD who are within 5 years from disease onset, despite the stability of spirometry parameters.

Similarly, clinical phenotype does not significantly influence participants in their decisions to initiate treatment for SSc-ILD, apart in situations where dcSSc is the only risk factor in patients with extensive ILD ('early dcSSc') (Figure 3(d)).

Other treatment options such as antifibrotic agents ($n = 2$) or ASCT are rarely selected by participants in the different clinical vignettes. ASCT is only cited in vignettes 6 ($n = 6$) and 7 ($n = 5$), which depict extensive ILD with worsening PFT in dcSSc within 5 years from disease onset.

## Discussion

Our study gives an overview of medical practices as expressed by clinicians managing SSc-ILD within the French context and before the approval of nintedanib in Europe and tocilizumab in the United States. To the best of our knowledge, it is the first study aiming to understand how specialists manage patients with SSc-ILD. Through a descriptive approach, we tried to identify challenges clinicians face when dealing with this complex disease for which treatment strategies are limited.

### *Diagnostic considerations and follow-up in SSc-ILD*

Clinicians systematically screen for ILD in SSc patients and this reflects national guidelines (*Protocole National de Diagnostic et de Soins (PNDS)* from 2017 and revised in 2020)[25] but also the recently published *European consensus statements*.[9] Resorting to PFT and chest CT scan is common practice for the screening of SSc-ILD at diagnosis.

Despite studies showing that ILD on the CT scan at baseline affects outcome in SSc, disparities in diagnostic approaches are still found with up to 11% of participants stating that systematic CT scans at baseline are unnecessary.[26] Prescription of CT chest scans is still not consensual through follow-up. Furthermore, only one third of

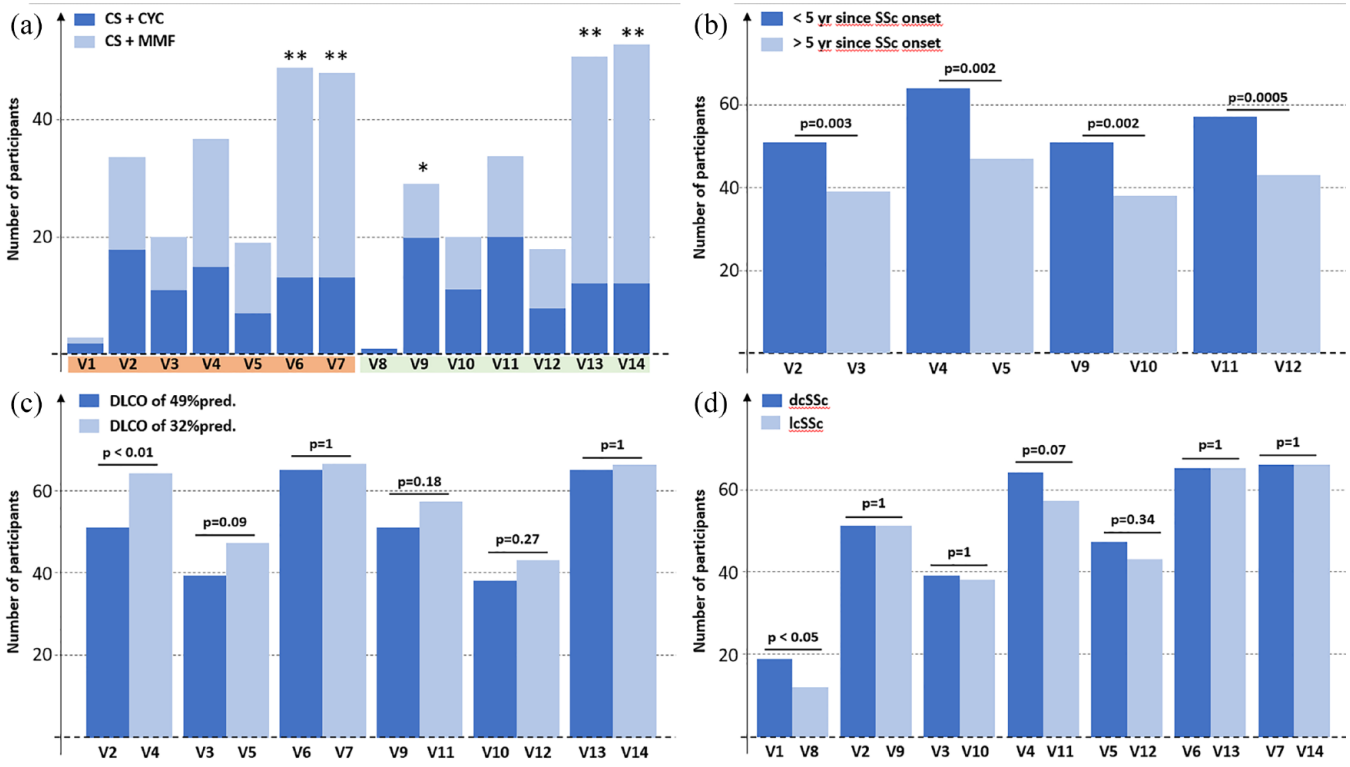


**Figure 3.** (a) Preferred treatment association for each clinical situation (vignette) according to participants. Vignettes (V1–V7) highlighted in pink refer to clinical situations studying dcSSc, and those highlighted in green (V8–V14) refer to lcSSc. Significant differences between treatment combinations are identified with asterisks: *$p < 0.05$ and **$p < 0.01$. (b) Comparison of the number of participants initiating treatment according to time from disease onset in patients with SSc-ILD with extensive ILD. (c) Comparison of the number of participants initiating treatment according to DLCO values in patients with SSc-ILD with extensive ILD. (d) Comparison of the number of participants initiating treatment according to dcSSc or lcSSc clinical phenotype in patients with limited ILD (V1 and V8) extensive ILD (V2–V14).
CS, corticosteroids; CYC, cyclophosphamide; MMF, mycophenolate mofetil.

participants use visual fibrotic scoring tools such as the one developed by Goh *et al.*[23] that also associates FVC threshold values to assess disease severity. Cutoff values for predicted FVC and DLCO are also poorly defined by clinicians (mostly clinical immunologists). Recommended threshold values for FVC and DLCO have been provided by national guidelines that define worsening of PFT as a relative decline of 10% in FVC over a 12- to 18-month period and/or a relative decline of 15% for DLCO over the same period.[25] Disparities in follow-up intervals for PFT also seem to be reflected by the latitude that is provided by such guidelines. Differences in answers relating to threshold values are once again due to the lack of consensual attitudes, although recent attempts have been made.[9] Interestingly, some percentage predicted FVC values given by participants (mostly clinical immunologists) were low by any standards.[27] As a recent French study found, FVC of less than 70%pred. and DLCO of less than 70%pred. are associated with poorer survival.[27] Adding to this are findings from studies suggesting that better treatment efficacy is achieved in patients with declining lung function[28–30] and highlighting the need to focus on patients with progressive SSc-ILD. Of note, pulmonologists were more likely to use higher cutoff values – reportedly for an earlier detection of ILD progression since mortality is known to inversely correlate with FVC – including in patients with normal-range baseline values.[26] In the absence of a clearcut consensus, French guidelines suggest performing PFT at least once a year (as do half of our respondents), while some authors suggest performing PFT every 4 to 6 months during the first 3 to 5 years from the time of SSc onset.[16,25,31] The interval between two consecutive follow-up PFT

in our survey ranged from 3 to 12 months reflecting disparities that may certainly be adjusted based on clinical context in daily practice.

Although none of the participants orders CPET at baseline, pulmonologists seem keener on referring patients to CPET during follow-up. It has been suggested that CPET could improve PAH detection with or without being combined with the DETECT score and may provide diagnostic and prognostic information for scleroderma patients presenting with multifactorial dyspnoea.[32–34]

Clinical and PFT worsening were the main reasons cited for ordering a chest CT scan, though some physicians did ask for systematic chest X-rays or CT scans regardless of whether patients presented with known ILD. Salaffi *et al.*[35] have shown that dyspnoea and PFT findings are correlated with the extent of pulmonary fibrosis on chest CT scans in SSc. Therefore, in the lack of better evidence for defining intervals between radiological procedures, it would appear that clinicians rely on features such as clinical phenotypes, functional status, progression of PFT parameters and previously established risk factors.[27,36,37] We did not evaluate the practice of lung sonography among our respondents, though it has been promoted by some authors as a potential tool for the diagnosis and the assessment of SSc-ILD and its progression, and may guide referral to CT scanning.[38,39]

Similarly, while some blood-based biomarkers such as CCL18 and Krebs von den Lungen-6 (KL-6) have been reported to be associated with ILD in SSc, and are suggested as diagnosis tools,[40,41] their use is not yet recognized in clinical practice by current French guidelines and therefore were not mentioned in our survey. Finally, MDT evaluation has become part of standard procedures for the diagnosis and management of ILD, especially in complex situations.[42] Due to the off-label use of many immunosuppressive drugs in SSc-ILD and the absence of well-defined criteria for treatment initiation, MDT meetings are useful for defining patient-centred treatment plans.

Of interest, self-reported experience in the management of SSc did not significantly modify attitudes for diagnosis, follow-up or treatment decisions. Since our study does not give us further insight, we hypothesize that less experienced practitioners tend to discuss patient management with their peers – thus highlighting the importance of a MDT approach.

### *Challenges in the management of SSc-ILD*

Many participants considered dyspnoea as a major criterion for deciding on whether to initiate treatment. PFT deterioration is also given precedence over ILD on CT scans. By considering patients' dyspnoea, causes other than ILD are assessed since patients with SSc can also present with PAH and/or limited exercise capacity due to peripheral impairment.[34] One could argue that in such circumstances CPET can be of use to avoid unnecessary procedures, including CT scans or right-heart catheterisation. Furthermore, Suliman *et al.*[43] have reported poor sensitivity of PFT for detecting early SSc-ILD: PFT need to be interpreted according to premorbid pulmonary function values, which are seldom available.[44] Clinicians are therefore more likely to suspect disease progression when patients complain of dyspnoea. Similarly, worsening DLCO and FVC were among the most cited criteria for initiating treatment, as highlighted by the clinical vignettes. This, however, was not the case for the percentage predicted DLCO value when participants were faced with clinical situations – albeit being cited by more than half of the participants as a key PFT parameter in the first part of the survey.

### *Treatment strategies as assessed by the clinical vignettes*

Discrepancies between the first part of the survey and the answers given for the vignettes were not easy to assess. However, there is a consensus among clinicians that worsening PFT is strong argument for initiating treatment for SSc-ILD, regardless of DLCO values, clinical phenotype (i.e. dcSSc or lcSSc) or the time from disease onset. The latter criterium was found to be a strong incentive for initiating treatments when the progression of SSc was less than 5 years from baseline (despite the stability of PFT), all other things being unchanged.

There was also a tendency to initiate treatment for lower DLCO values, though the difference between 32% and 49% of predicted DLCO in treatment initiation was rarely significant. Participants having set a median cutoff value for percentage predicted DLCO at 70%, it is possible that attitudes may have been different had we selected higher PFT values for the clinical vignettes.

Therapeutic approaches were consistent throughout the survey and vignettes regarding

corticosteroids. In keeping with expert consensus statements, steroids were hardly ever prescribed as standalone therapies for SSc-ILD.[9] Since high-dose corticosteroid has been show to possibly precipitate scleroderma renal crisis, it was unwaited that 13 participants prescribed doses greater than 15 mg q.d. for the treatment of SSc-ILD.[45]

On the other hand, participants who showed no preference for either MMF or CYC as first-line treatments were found to prescribe CYC more often when faced with worsening PFT in the clinical vignettes. This might reflect ingrained notions that CYC may have a quicker effect on ILD despite data from successive studies showing that short-term and long-term efficacy MMF is not inferior to CYC.[30] These attitudes might change with the recent findings from the SENSCIS trial where encouraging results have been described in the subgroup analysis of the efficacy and tolerance of a combination therapy of MMF and nintedanib.[46]

Not unlike nintedanib, tocilizumab was only exceptionally mentioned as a possible treatment for progressive SSc-ILD. This could reflect the lack of exposure of participants to this treatment since the results of the focuSSced trial had not been made public at the time.[47] The secondary endpoint of the focuSSced study suggested that tocilizumab might preserve lung function in people with early SSc-ILD and elevated acute phase reactants. Of interest, consensus was not reached regarding its use in the European consensus statement.[9] On the other hand, rituximab has been positioned as a third-line therapy, due to its relative safety and efficacy in SSc-ILD.[48–50] High-dose immunosuppressant therapy with ASCT has been recommended by EULAR for selected patients with rapidly progressive SSc at risk of organ failure.[15] This option, just as lung transplantation, was only adopted on occasion despite there being up to a quarter of participants with some experience in the management of transplanted scleroderma patients.

Participants rated the overall effectiveness of current treatments as 'moderate', illustrating the extent to which better options are needed to improve patients' survival and quality of life.

### *Drawbacks and pitfalls*

One of the major drawbacks of our study is possibly the limited participation by other specialists (i.e. rheumatologists) but reflects cultural differences with other countries since SSc-ILD is mostly managed by clinical immunologists and respiratory specialists in France. Another aspect was that this study was promoted primarily through networks of internists and pulmonologists.

Choices had to be made when writing the clinical vignettes. The latter had to focus on a limited set of clinical and PFT features in order to get a better grasp of participants' therapeutic attitudes. Risk factors for disease progression such as age, sex, ethnicity or inflammatory markers were not featured so as not to add complexity to the decision-making process and keep the number of vignettes down to 14.[31,51] Similarly, the intensity of symptoms and description of ILD CT-scan patterns were not presented. Furthermore, assessing quality of life in SSc-ILD is somewhat of a challenge due to the design of our online survey. Tools such as the *Saint George's Respiratory Questionnaire* (that have been validated in SSc-ILD) could be assimilated into daily practice to provide treatment objectives centred on patients' quality of life.[52]

Of note, there was no incentive given to participants for them to complete the entire survey that takes around 20 minutes. We thus relied on the goodwill of the participants – some of whom took the time to answer the survey in the midst of a pandemic – and to whom we are extremely grateful.

Our survey was terminated prior to the release of the results from the SENSCIS trial evaluating the safety and tolerability of nintedanib in patients with SSc-ILD.[53] This most probably explains the hesitancy of many, mostly non-respiratory specialists, to prescribe an antifibrotic drug such as nintedanib in an off-label use. The impact of such treatment would require a few years to be appropriately assessed.

## Conclusion

This study presents an overview of the way specialists approach the diagnosis, follow-up and treatment of SSc-ILD in France. It aimed to assess the implementation of current guidelines and expert consensus statements and how it reflects on patient management from a practical standpoint. The complexity and diversity of clinical, immunological and pathological phenotypes have been obstacles for effective treatment procedures. Points of interest have been highlighted *via* our survey to improve and harmonize practices at the dawn of a new era of therapies in SSc and SSc-ILD.

## Declaration

### *Ethics approval and consent to participate*

Our study complies with Institutional ethical standards and those of the national research committee. For this type of study, authorization from an Institutional Review Board was not required and all collected data were de-identified in compliance with French Regulation. Storage of data was done in accordance with *Commission Nationale de l'Informatique et des Libertés* (CNIL) guidelines.

### *Consent for publication*

All participants and authors gave consent for publication.

### *Author contributions*

**Amélie Nicolas:** Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

**Sylvie Leroy:** Conceptualization; Investigation; Writing – review & editing.

**Luc Mouthon:** Conceptualization; Writing – review & editing.

**Yurdagul Uzunhan:** Conceptualization; Writing – review & editing.

**Vincent Cottin:** Conceptualization; Writing – review & editing.

**Arsene Mekinian:** Conceptualization; Writing – review & editing.

**Viviane Queyrel:** Conceptualization; Writing – review & editing.

**Eric Hachulla:** Conceptualization; Writing – review & editing.

**Benoit Gachet:** Formal analysis; Writing – review & editing.

**David Launay:** Conceptualization; Methodology; Validation; Writing – review & editing.

**Nihal Martis:** Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

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### *Competing interests*

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### *Availability of data and material*

The survey used for this study is available in Supplementary Data. Original data are available by asking corresponding author.

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**Supplemental material**
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