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Expert consensus on the management of systemic sclerosis-associated interstitial lung disease

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Abstract

**Background** Systemic sclerosis (SSc) is a rare, complex, connective tissue disorder. Interstitial lung disease (ILD) is common in SSc, occurring in 35-52% of patients and accounting for 20-40% of mortality. Evolution of therapeu­tic options has resulted in a lack of consensus on how to manage this condition. This Delphi study was initiated to develop consensus recommendations based on expert physician insights regarding screening, progression, treatment criteria, monitoring of response, and the role of recent therapeutic advances with antifibrotics and immunosuppres­sants in patients with SSc-ILD.

**Methods** A modified Delphi process was completed by pulmonologists (n = 13) and rheumatologists (n = 12) with expertise in the management of patients with SSc-ILD. Panelists rated their agreement with each statement on a Lik­ert scale from — 5 (complete disagreement) to + 5 (complete agreement). Consensus was predefined as a mean Likert scale score of < — 2.5 or > + 2.5 with a standard deviation not crossing zero.

**Results** Panelists recommended that all patients with SSc be screened for ILD by chest auscultation, spirometry with diffusing capacity of the lungs for carbon monoxide, high-resolution computed tomography (HRCT), and/or autoanti­body testing. Treatment decisions were influenced by baseline and changes in pulmonary function tests, extent of ILD on HRCT, duration and degree of dyspnea, presence of pulmonary hypertension, and potential contribution of reflux. Treatment success was defined as stabilization or improvement of signs or symptoms of ILD and functional status. Mycophenolate mofetil was identified as the initial treatment of choice. Experts considered nintedanib a therapeu­tic option in patients with progressive fibrotic ILD despite immunosuppressive therapy or patients contraindicated/ unable to tolerate immunotherapy. Concomitant use of nintedanib with MMF/cyclophosphamide can be considered in patients with advanced disease at initial presentation, aggressive ILD, or significant disease progression. Although limited consensus was achieved on the use of tocilizumab, the experts considered it a therapeutic option for patients with early SSc and ILD with elevated acute-phase reactants.

BMC

**Conclusions** This modified Delphi study generated consensus recommendations for management of patients with SSc-ILD in a real-world setting. Findings from this study provide a management algorithm that will be helpful for treat­ing patients with SSc-ILD and addresses a significant unmet need.

**Keywords** Autoimmune diseases, Connective tissue diseases, Pulmonary fibrosis, Drug therapy, Algorithms

Background

Systemic sclerosis (SSc) is a rare, complex connec­tive tissue disease of unknown etiology characterized by microvascular damage, dysregulation of innate and adaptive immunity, and generalized fibrosis in the skin and multiple internal organs [[1](#bookmark82)-[3](#bookmark89)]. It can target many organ systems, including the skin, lungs, heart, blood vessels, kidneys, gastrointestinal tract, and musculoskel­etal system [[2](#bookmark86), [3](#bookmark89)]. While the pathogenesis of SSc is not well understood, hallmarks include inflammation, vascu­lopathy, and fibroblast dysfunction. Risk factors associ­ated with the development of and/or progression of ILD include male sex, African-American race, diffuse cuta­neous SSc (dcSSc), presence of anti-Scl-70/anti-topoi- somerase I antibodies, and cardiac involvement [[4](#bookmark91)-[6](#bookmark94)].

Interstitial lung disease (ILD) occurs in 35-52% of patients with SSc and accounts for 20-40% of mortal­ity [[7](#bookmark96)-[10](#bookmark101)]. The risk of developing ILD is greatest early in the course of SSc, and timely detection is important for monitoring progression and informing therapeutic deci­sion-making [[4](#bookmark91), [11](#bookmark103)]. A European consensus statement identified chest high-resolution computed tomography (HRCT) as the primary diagnostic tool for SSc-ILD, sup­ported by pulmonary function tests (PFTs) for screen­ing and diagnosis [[12](#bookmark105)]. Declining values for forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLco) can suggest progression of ILD [[1](#bookmark82), [4](#bookmark91), [13](#bookmark107)].

The European League Against Rheumatism (EULAR) guidelines for the management of SSc recommend cyclophosphamide (CYC) for the treatment of SSc-ILD. Hematopoietic stem cell transplantation may also be con­sidered in patients with rapidly progressive SSc at risk of organ failure, although careful selection of patients is required due to a high risk of treatment-related side effects and mortality [[14](#bookmark109)-[16](#bookmark112)]. Mycophenolate mofetil (MMF) provides similar efficacy to CYC and is associ­ated with less toxicity [[17](#bookmark114)-[21](#bookmark121)]. For patients who do not respond to treatment, lung transplantation may be a life­saving option [[22](#bookmark123), [23](#bookmark125)].

Antifibrotic drugs represent another class that may be considered a potential treatment option for SSc-ILD based on their efficacy in idiopathic pulmonary fibrosis (IPF), a condition with pathogenic similarities. Nint- edanib has been approved for the treatment of SSc-ILD and chronic fibrosing ILDs with a progressive phenotype based on the results of the SENSCIS and INBUILD tri­als respectively [[24](#bookmark127)-[26](#bookmark131)]; pirfenidone is currently under evaluation [[27](#bookmark133), [28](#bookmark135)]. In addition, tocilizumab (TCZ), an inhibitor of interleukin-6, has recently been approved for the treatment of SSc-ILD based on the results of the focuSSced trial [[29](#bookmark137), [30](#bookmark139)].

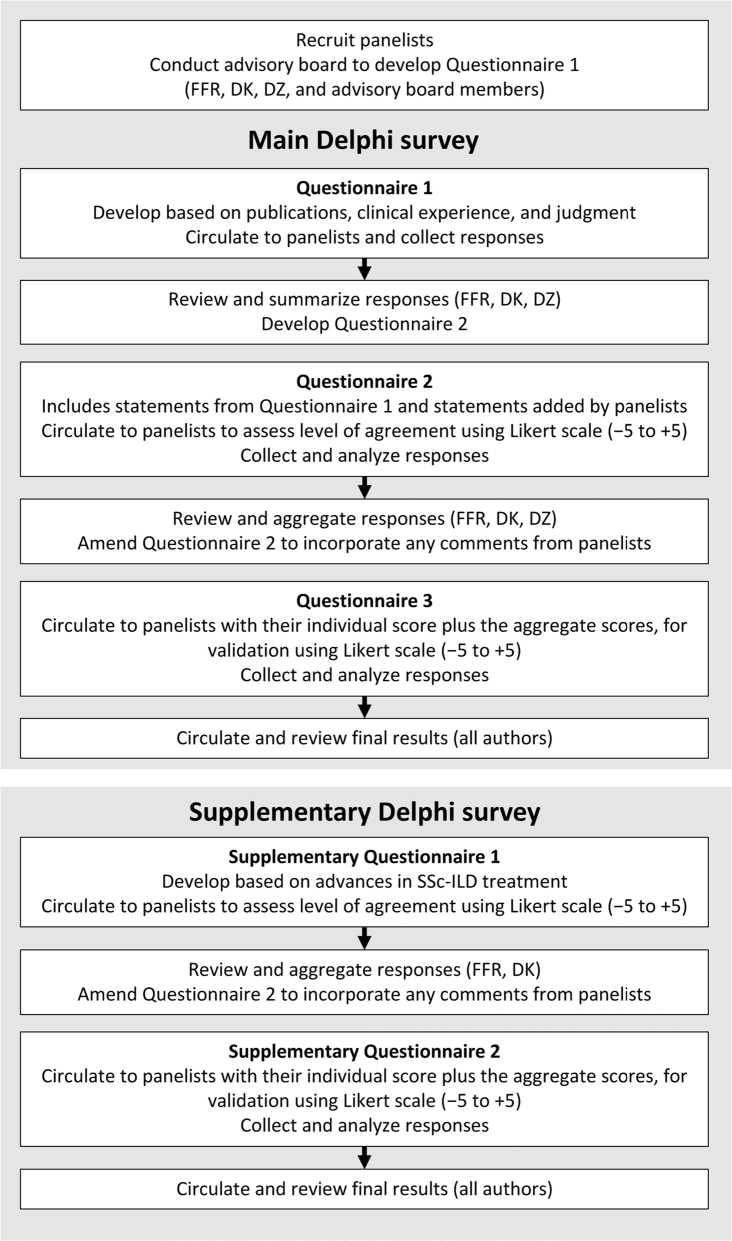
There is a growing desire among pulmonologists and rheumatologists to identify screening, detection, and monitoring strategies that are clinically meaningful and improve patient outcomes. The objective of this Delphi study was to develop consensus recommendations based on expert physician insights regarding screening, disease progression, treatment criteria, monitoring of therapeu­tic response, and the potential future role of antifibrotics in the treatment paradigm for patients with SSc-ILD.

Methods

This modified Delphi process was conceived and initiated by the lead and corresponding authors (FFR and DK). As moderators, FFR and DK worked with an advisory board of pulmonologists and rheumatologists with experience in treating SSc-ILD, and Boehringer Ingelheim Pharma­ceuticals Inc., to determine the panel selection criteria and identify potential members.

The modified Delphi process followed in this study was as follows (Fig. [1](#bookmark18)):

1. The moderators and advisory board members devel­oped Questionnaire 1 based on current clinical prac­tice, a review of the literature, and clinical experience. This topically organized questionnaire included mul­tiple statements relevant to screening, treatment cri­teria, and the potential role for antifibrotic drugs in patients with SSc-ILD. These topics were maintained through all three questionnaires. The Questionnaire was circulated via an online survey platform (Survey- gizmo.com) to the Delphi panelists, who provided their independent comments for each statement and added additional statements at their discretion.
2. Following review of the aggregate anonymized responses to Questionnaire 1, the moderators devel­oped Questionnaire 2, which incorporated both the initial and additional statements from the panelists. Questionnaire 2 was circulated using the same online survey platform and the panelists rated each state­ment using a Likert scale ranging from -5 (strongly



**Fig. 1** The Delphi process employed for both the first and second Delphi analyses. *SSc-ILD* systemic sclerosis-associated interstitial lung disease

disagree) to + 5 (strongly agree). Consensus was defined prospectively as a mean rating of < -2.5 or > + 2.5, with a standard deviation (SD) that did not cross zero.

1. The moderators refined the statements based on the aggregate results from Questionnaire 2 to cre­ate the 152-statement Questionnaire 3, again circu­lated using the online survey platform. To promote consensus 'for' or 'against' each statement, panelists also received separately their individual responses to Questionnaire 2 plus the panel's aggregate results (mean and SD). Additional questions regarding the role of nintedanib in the treatment of SSc-ILD were shared with the panel following publication of the SENSCIS trial results.
2. The aggregate results of Questionnaire 3 were circu­lated to the panelists for final review and comment (see Additional file [1](#bookmark78): Table SI for details).
3. Following publication of the INBUILD, RELIEF, and focuSSced trial results [[25](#bookmark129), [27](#bookmark133), [29](#bookmark137)], a supplementary Delphi survey comprising two questionnaires focus­ing on the current treatment paradigm was con­ducted. The same approach was used as described above.

Panelists' anonymity was ensured throughout the study to prevent bias induced by influential clinicians and help ensure that all panelists were comfortable offering their opinions freely. Panelists were encouraged to provide feedback on the validity, specificity, and content of the items under consideration.

Results

The Delphi process was initiated in 2018 with a panel comprising 25 physicians (Table [1](#bookmark49)). The panel included 13 pulmonologists and 12 rheumatologists practicing pre­dominately in academic centers (n = 24), hospital-based clinics (n = 3), and Veterans Administration (n = 2). Some panelists practiced across multiple care settings. Their collective experience of seeing patients with SSc-ILD was 16.68 士 9.68 (mean 士 SD) years, treating 80.04 士 73.23 patients with SSc-ILD in the last year (Table [1](#bookmark49)). The panel reached consensus on 109 of the 239 statements (45.6%); 98 statements reached consensus 'for' and 11 reached consensus ‘against.' A list of all questions and results from Questionnaire 3 and Supplementary Questionnaire 2 can be viewed in Additional file [1](#bookmark78): Tables S1 and S2.

Screening

Panelists recommended the use of chest auscultation, full PFTs, spirometry with DL**CO**, HRCT, and autoanti­body testing to screen patients with SSc for ILD (Fig. [2](#bookmark50), Additional file [1](#bookmark78): Table S1). The consensus was that all patients with SSc should be screened, with greater agree­ment for patients with respiratory symptoms and those at high risk (e.g. dcSSc, positive for Scl-70 antibodies, Afri­can-American ethnicity, and/or a high modified Rodnan skin score [mRSS]). In addition, panelists recommended routinely screening for pulmonary hypertension (PH) in patients with SSc; the consensus to screen for this was even stronger when shortness of breath not explained by progression of ILD is observed.

**Table 1** Characteristics of the Delphi panelists

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Number of panelists** | **Mean** 土 **SD** |
| Specialty |  |  |
| Pulmonology | 13 |  |
| Rheumatology | 12 |  |
| Experience treating SSc-ILD (n = 25) |  | 16.68 土 9.68 |
| < 10 years | 6 |  |
| 11-20 years | 14 |  |
| > 20 years | 5 |  |
| Patients with SSc-ILD treated in entire career (n = 24) |  | 369.58 土 341.74 |
| < 500 | 21 |  |
| 501-1000 | 2 |  |
| > 1000 | 1 |  |
| Patients with SSc-ILD treated last year (n = 23) |  | 80.04 土 73.23 |
| < 50 | 11 |  |
| 51-150 | 10 |  |
| > 150 | 2 |  |

*SD* standard deviation, *SSc-ILD* systemic sclerosis-associated interstitial lung disease

|  |  |  |  |
| --- | --- | --- | --- |
| Statement | Mean | SD |  |
| Screening for the general scleroderma population for ILD should include: |  |  |  |
| Chest auscultation |  |  | i ■ |
| 4.32 | 1.18 | **1** |
| PFTs | 4.16 | 1 70 | : : . |
| Spirometry with DLC0 | 4.36 | 1.04 | **1** |
| HRCT | 4.08 | 1.63 | **1**  **1** |
| Autoantibody testing | 2.96 | 1.79 | **1** |
| Considerations in determining which patients to screen/diagnose for ILD include:  All SSc patients | 3.72 | 2.19 |  |
| **1** |
| Patients with symptoms | 4.92 | 0.28 | **■1** |
| High-risk patients (eg: dcSSc, +Scl-70 antibodies, African American ethnicity, and/or high modified Rodnan skin score) | 4.96 | 0.20 |  |
| *When to screen for pulmonary hypertension in patients with SSc-ILD\** |  |  |  |
| *Once per year* | *4.41* | *0.85* | **:::-F** |
| *1 routinely screen for pulmonary hypertension* | *4.59* | *0.73* |  |
| *1 screen for pulmonary hypertension when shortness of breath is not explained by progression of ILD* | *4.86* | *0.47* |  |
| *1 do not screen for pulmonary hypertension* | *-4.77* | *0.53* | t; ——] |

-5.0 -2.5 0.0 2.5 5.0

Mean Delphi score

**Disagree ◄ ► Agree**

**Fig. 2** Consensus recommendations for screening criteria for SSc-ILD. \*Data from the 2022 supplementary Delphi. *dcSSc* diffuse cutaneous systemic sclerosis, *DLC0* diffusing capacity of the lungs for carbon monoxide, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *PFT*pulmonary function test, *SD* standard deviation, *SSc* systemic sclerosis

Treatment criteria

Panelists reached consensus that their treatment deci­sions were influenced by baseline and clinically meaning­ful changes in PFT values, the extent of ILD or fibrosis on HRCT, the duration and degree of dyspnea, the presence of PH, and the potential contribution of reflux (Fig. [3](#bookmark51)). There was no consensus regarding the use of autoanti­body status, age, presence of comorbidities, or duration of disease (Additional file [1](#bookmark78): Table S1). The panelists recom­mended that treatment should be initiated in patients with abnormal or progressive findings on HRCT, FVC < 80%, or FVC > 80% if accompanied by ILD in a high-risk patient or by dyspnea, by a notable decline in FVC, or accompanied by peripheral capillary oxygen desaturation (SpO**2**) on exer­cise (Fig. [3](#bookmark51)). Moderate-to-severe ILD on HRCT (or > 20% lung involvement), FVC and/or DL。。below the normal lower limit, moderate-to-severe symptoms, early rap­idly progressive dcSSc (even if accompanied by only mild abnormalities on HRCT and/or PFTs), hypoxemia at rest, and desaturation on exercise were considered sufficiently concerning to warrant immediate treatment. The panel also reached consensus that patients with longstanding

disease (close to 10 years), stable PFTs, and no progression of ILD over recent years should not be treated (Additional file [1](#bookmark78): Table S1).

Treatment sequencing

Panelists considered MMF as first-line therapy for patients with SSc-ILD at a target dose of 2000-3000 mg daily. Ini­tial nintedanib therapy, at a target dose of 150 mg twice daily, was recommended for patients with longstanding (> 5 years) SSc with ILD and evidence of progression for whom immunosuppression would not be recommended. (Fig. [4](#bookmark52)A, Additional file [1](#bookmark78): Table S2). It was also considered as add-on therapy to MMF or CYC and following failure of MMF, CYC, and/or TCZ. However, there was no consensus on the use of CYC, rituximab, azathioprine, prednisone, or TCZ as initial therapy, nor for the use of nintedanib as initial therapy in patients other than those previously described (Additional file [1](#bookmark78): Table S1). There was consen­sus against utilizing methotrexate as initial therapy for patients with SSc-ILD, and there was no consensus on the duration of treatment.

Mean SD

Statement

Considerations in deciding whether to treat patients for ILD include:

Moderate-to-severe ILD on HRCT

| Extent of ILD or fibrosis on HRCT | 4.56 | 1.08 |
| --- | --- | --- |
| Baseline PFT values | 4.08 | 0.95 |
| Clinically meaningful change (decline) in PFT values | 4.76 | 0.52 |
| Duration and degree of dyspnea | 3.76 | 1.36 |
| Potential contribution of reflux | 2.52 | 1.58 |
| Presence of pulmonary hypertension | 3.08 | 1.63 |
| Based on HRCT, patients are treated who have: |  |  |
| Worsening HRCT with symptoms or declining PFTs | 4.84 | 0.37 |
| >20% total lung involvement on HRCT with normal PFTs | 3.04 | 1.57 |
| >20% total lung involvement on HRCT with abnormal PFTs | 4.48 | 0.82 |
| >10% total lung involvement on HRCT with abnormal PFTs | 3.52 | 1.29 |
| High-risk patients (early diffuse disease) with evidence of mild ILD (<10%) and abnormal PFTs | 4.08 | 1.12 |
| High-risk patients (early diffuse disease) with evidence of mild ILD (<10%) | 3.24 | 1.51 |
| Based on FVC and symptom status (assume all patients have ILD on HRCT), patients are treated who have: |  |  |
| FVC >80% with ILD on HRCT in a high-risk patient (early diffuse disease, Topo+) | 3.72 | 1.51 |
| FVC <80% with any degree of ILD on HRCT | 2.68 | 1.80 |
| FVC <80% and dyspnea | 3.44 | 1.50 |
| FVC <70% and dyspnea | 4.12 | 1.24 |
| Decline in FVC by greater than measurement error (5-7%) | 4.16 | 0.90 |
| Decline in FVC by >10% in 1 year | 4.48 | 0.87 |
| Besides HRCT and PFTs, other treatment parameters to consider when initiating treatment include: |  |  |
| Exertional desaturation on SpO2 | 3.28 | 1.54 |

Patients who should NOT be treated for SSc-ILD include:

| Patients with longstanding disease (close to 10 years), stable PFTs and no progression of ILD over last few years  Criteria to determine the phenotype of patients who are likely to respond to treatment include: | 3.52 | 1.81 |
| --- | --- | --- |
| Findings or changes on HRCT | 3.84 | 1.31 |
| Findings or changes on PFTs | 3.68 | 1.35 |
| Duration of symptoms | 2.72 | 1.54 |
| Consideration of autoantibodies in deciding whether to treat patients for SSc-ILD at initial presentation should include: Patients with other antibodies than U1 RNP or no specific antibodies have to be taken individually as we don't know | 2.76 | 2.19 |

how aggressive their disease will be

/zAt initial presentation in patients with SSc, this condition would cause me enough concern about near-term ILD that I would start treatment right away":

FVC and/or DLc0<LLN

Moderate to severe symptoms

Early, rapidly progressive diffuse subset even with mild abnormalities on HRCT chest scan

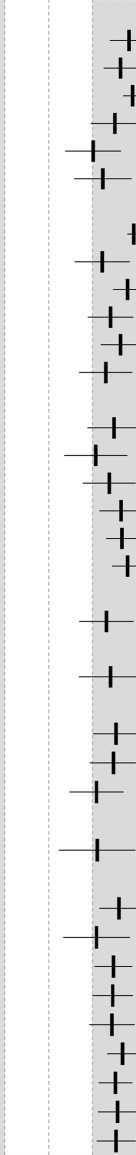
Early, rapidly progressive diffuse subset even with mild abnormalities on PFT

Early, rapidly progressive diffuse subset even with mild abnormalities on HRCT chest scan AND mild abnormalities on PFT

HRCT showing ILD >20% lung involvement

Hypoxia at rest

Desaturation on exercise

-5.0 -2.5 0.0 2.5 5.0

4.00 1.12

2.72 1.90

3.68 1.07

3.64 1.15

3.60 1.29

4.20 0.87

3.80 0.96

3.92 1.12

3.84 1.11

Mean Delphi score

Disagree ◄ ► Agree

**Fig. 3** Consensus recommendations for SSc-ILD treatment criteria. *dcSSc* diffuse cutaneous SSc, *DLC0* diffusing capacity of the lungs for carbon monoxide, *FVC*forced vital capacity, *HRCT*high-resolution computed tomography, *ILD* interstitial lung disease, *LLN* lower limit of normal,

*PFT*pulmonary function test, *RNP* ribonucleoprotein, *SD* standard deviation, *SpO?* peripheral capillary oxygen saturation, *SSc* systemic sclerosis, *Topo* topoisomerase

Based on the following response to SSc-ILD treatment, please indicate your likely course of action:

The potential role of antifibrotic drugs

When asked how the panel's treatment choices for patients with SSc-ILD have changed since publication of the SENS- CIS, INBUILD, and focuSSced trial results, 77% mentioned that they had increased their use of nintedanib or antifi- brotics, while 45% mentioned that they now use or would consider using TCZ.

Antifibrotic drugs in general were considered poten­tial therapeutic options based on a decline in PFTs and/or HRCT, and it was recommended that they should be used in combination with or after MMF/CYC. Following the results of the SENSCIS and INBUILD trials, the panelists reached consensus that nintedanib specifically was a ther­apeutic option for patients with progressive fibrotic ILD despite immunosuppressive therapy, both as monotherapy and in combination with MMF/CYC/TCZ, for patients with aggressive ILD (defined as relative FVC decline > 10% in 1 year), with advanced disease at initial presentation (FVC <50%) in combination with MMF/CYC/TCZ, and for patients with contraindications to or who are unable to tolerate immunosuppression (MMF/CYC/TCZ). There was also consensus that nintedanib could be used to treat patients unable to continue with MMF, CYC, or TCZ due to adverse effects or lack of efficacy with the effective dose

(Fig. [4](#bookmark52)B, Additional file [1](#bookmark78): Table S2). The panelists' con­sensus was that the decision to include nintedanib in the treatment regimen should be based on lack of an effective response to MMF/CYC/TCZ, defined by a combined lack of improvement in symptoms, HRCT, and/or PFT results, or an active worsening of the patient's condition, defined by worsening of ILD on HRCT, worsening of lung function, or a combination of the two with worsening symptoms.

The potential role of TCZ

Following the results of the focuSSced trial, the panelists agreed that TCZ should be considered in patients with early SSc and ILD with elevated acute-phase reactants. Use of TCZ in patients experiencing worsening on initial ther­apy did not achieve consensus by the whole group. They also considered TCZ an option for patients unable to con­tinue CYC, MMF, or antifibrotics due to adverse effects. There was no consensus agreement on how TCZ fits into the management of SSc-ILD (Fig. [4](#bookmark52)B, Additional file [1](#bookmark78): Table S2).

Management of disease progression

Panelists reached consensus on the possibility of adding further agents for patients with progression/worsening of

| MMF | 4.72 | 0.74 |
| --- | --- | --- |
| Methotrexate | -2.84 | 2.48 |
| The typical/target dose for MMF is: |  |  |
| 2000 mg daily | 2.68 | 1.82 |
| 3000 mg daily | 4.44 | 0.77 |
| 1 do not utilize MMF | -4.56 | 1.39 |
| The typical/target dose for azathioprine is: |  |  |
| 2-3 mg/kg/day | 2.88 | 2.46 |
| The typical/target dose for rituximab is: |  |  |
| 1 g on days 0 and 15, then every 6-12 months | 2.76 | 2.49 |
| 1 do not utilize rituximab | -2.76 | 2.70 |
| *The typical/target dose for nintedanib is:\** |  |  |
| *150 mg twice daily* | *4.68* | *0.57* |
| *1 do not utilize nintedanib* | *-4.73* | *0.55* |
| *The typical/target dose for TCZ is:\** |  |  |
| *162 mg/week* | *4.18* | *1.44* |
| *1 do not utilize TCZ* | *-3.36* | *1.89* |

**A** Statement

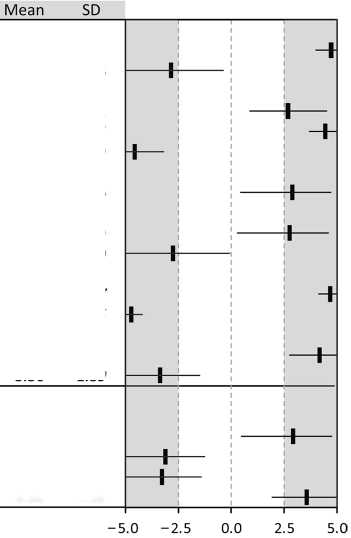
The initial therapy used to treat SSc-ILD is:

With progression/worsening of ILD, I would add another agent

With stability of ILD, I would switch to another agent

With stability of ILD, I would add another agent

With stability of ILD, I would continue treatment as is

Mean Delphi score

| 2.92 | 2.66 |
| --- | --- |
| -3.12 | 1.88 |
| -3.28 | 1.88 |
| 3.56 | 1.85 |

Disagree ◄ ► Agree

**Fig. 4** Consensus recommendations for SSc-ILD treatment paradigm. **A** Treatment dosage and next steps following treatment response. **B** Use of nintedanib and tocilizumab. \*Data from the 2022 supplementary Delphi. ^Consensus was not reached in main Delphi analysis. *CYC* cyclophosphamide, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *MMF* mycophenolate mofetil, *PFT*pulmonary function test, *SD* standard deviation, *SSc* systemic sclerosis, *TCZ*tocilizumab

**B** Statement

Nintedanib fits into the management of SSc-ILD as follows: *As initial therapy for patients with longstanding SSc (>5 years) with ILD and evidence of progression for whom immunosuppression would not be recommended\** Add-on therapy after failure of

I

I would use nintedanib under the following conditions:

| MMF/CYC | 3.40 | 1.71 |
| --- | --- | --- |
| *MMF\** | *3.82* | *0.66* |
| *CYC\** | *3.64* | *0.79* |
| *MMF and CYC\** | *3.82* | *0.73* |
| *TCZ\** | *3.00* | *1.93* |
| *TCZ and CYC\** | *3.59* | *0.73* |
| *TCZ and MMF\** | *3.64* | *0.66* |
| *TCZ and MMF and CYC\** | *3.64* | *0.58* |
| *Add-on therapy to MMF/CYC\** | *3.77* | *0.81* |

Patients with progressive fibrotic ILD despite

Immunosuppressive therapy

*Immunosuppressive therapy (MMF/CYC/TCZ)\**

Patients with progressive fibrotic ILD in combination with MMF/CYC

*MMF/CYC/TCZ\**

Patients who have contraindications to or are unable to tolerate

Immunosuppression

*Immunosuppression (MMF/CYC/TCZ) \**

For patients with aggressive ILDZ advanced disease at initial presentation, or significant disease progression

In combination with immunosuppressive agents (MMF/CYC)

*In combination with immunosuppressive agents (MMF/CYC/TCZ) \**

Lack of effective response or improvement with immunosuppressive agents as defined by lack of improvement of lung function

MMF/CYC

*MMF/CYC/TCZ\**

Lack of effective response or improvement with immunosuppressive agents, defined by a combination of no improvement in symptoms; ILD on HRCT; and/or PFTs

MMF/CYC

*MMF/CYC/TCZ\**

Based on inability to continue immunosuppressive treatment due to adverse effects

MMF/CYC

*MMF/CYC/TCZ\**

Based on inability to continue immunosuppressive treatment due to lack of achievement of effective dose

MMF/CYC

*MMF/CYC/TCZ\**

*Active worsening of the patient's condition, defined by worsening of ILD on HRCT\**

*Active worsening of the patient's condition,*

*defined by worsening of lung function\**

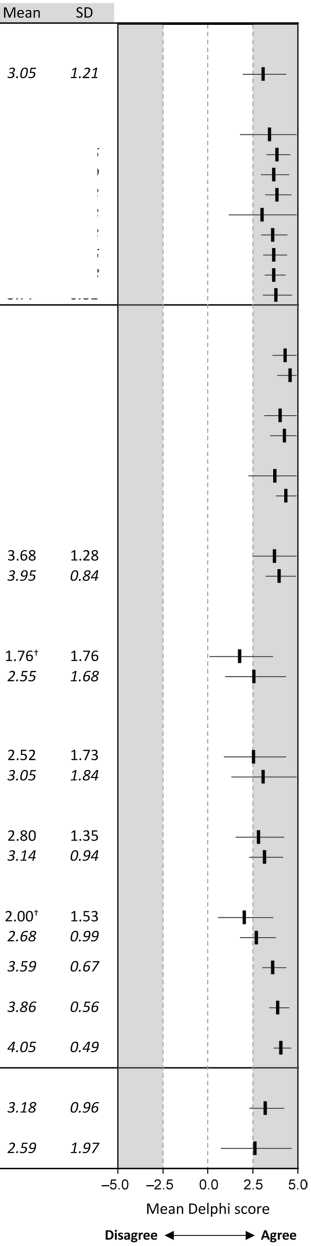
*Active worsening of the patient's condition, defined by*

*a combination of worsening symptoms; ILD on HRCT; and/or PFTs\**

*I would use TCZ under the following conditions:\**

*Patients with early SSc and ILD with elevated acute­phase reactants*

*Based on inability to continue CYC/MMF/antifibrotics due to adverse effects*

**Fig. 4** continued

| 4.28 | 0.79 |
| --- | --- |
| *4.55* | *0.80* |
| 4.00 | 0.96 |
| *4.23* | *0.87* |
| 3.71 | 1.55 |
| *4.32* | *0.65* |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Statement | Mean | SD | | |
| The following circumstances would prompt weaning a patient from therapy: |  |  |  |  |
| Toxicity to the drug (including side effects and adverse | 4.08 | 1.00 |  | **1** |
| events)  Stability for >2 years in lung as well as skin |  |  |
| 3.04 | 2.30 |
| *i* i | **1** |
| Patient's strong desire to discontinue treatment | 3.60 | 1.66 |
|  | **1** |
| Lack of efficacy | 3.20 | 2.25 |
|  | **1** |
| Patients are typically weaned from therapy as follows: |  |  | 1 1 1 |  |
| Taper/wean over 1-2 years, monitor PFTs every 6 months, | 3.56 | 1.66 |  | **1** |
| with or without low maintenance dose of MMF Taper/wean over months to a year to a lower maintenance | « ； T | **I** |
| 2.60 | 1.47 |
| dose  Stop therapy quickly (over weeks or "cold turkey") | **1**  **i :** |  |
| -3.28 | 2.51 |
| **I** |  |

-5.0 -2.5 0.0 2.5 5.0

Mean Delphi score

**Disagree ◄ ► Agree**

**Fig. 5** Consensus recommendations for duration of SSc-ILD treatment. *MMF* mycophenolate mofetil, *PFT*pulmonary function test, *SD* standard deviation, *SSc-ILD* systemic sclerosis-associated interstitial lung disease

ILD, but did not reach consensus on switching to another agent or continuing therapy under these circumstances. Panelists agreed that patients should be weaned from therapy in cases of drug toxicity, stable lung and skin symptoms for > 2 years, a patient's strong desire to dis­continue treatment, or lack of efficacy (Fig. [5](#bookmark53)). Tapering/ weaning therapy should take place over 1-2 years while monitoring PFTs every 6 months, with or without a low maintenance dose of MMF, and treatment should not be withdrawn abruptly.

Consensus was reached that disease progression should be monitored using changes in PFTs (FVC or DLco), HRCT (ILD patterns or extent of fibrosis), and symp­toms over time, or by presence of desaturation on exer­cise (Fig. [6](#bookmark54)). Conversely, stabilization or improvement of FVC, DLco, HRCT, or 6-min walk distance (6MWD), stabilization of symptoms, level of desaturation on exer­cise, and functional status as assessed by New York Heart Association Functional Classification or cardiopulmo­nary exercise testing were indicative of treatment success (Fig. [6](#bookmark54), Additional file [1](#bookmark78): Table S1).

Management approach based on specialty

There were subtle differences in responses between rheu­matologists and pulmonologists (Table [2](#bookmark55)). Pulmonolo­gists achieved consensus in favor of assessing 6MWD for screening, deciding whether to treat, and defining

treatment success, whereas rheumatologists did not rate this assessment so highly. Conversely, pulmonologists did not reach consensus on whether FVC and/or DL。。below the lower limit of normal would prompt immediate treat­ment. Pulmonologists aligned with panel consensus sup­porting consideration of reflux when deciding whether to treat; rheumatologists aligned with the panel against the use of methotrexate as an initial treatment option for SSc-ILD. Although both groups agreed that MMF should be the initial treatment of choice, rheumatologists were more comfortable using rituximab as potential therapy.

The potential use of antifibrotic drugs was more strongly supported by pulmonologists than by rheu­matologists. Pulmonologists (but not rheumatologists) achieved consensus for the use of nintedanib in patients with a lack of response to MMF, CYC, or TCZ as defined by no improvement in lung function, and in any patients with connective tissue disease with clinically signifi­cant or worsening ILD. Conversely, there was consensus amongst only rheumatologists that nintedanib could be used as add-on therapy to TCZ.

overall, rheumatologists were more comfortable than pulmonologists with defining how TCZ should be used as a treatment option for SSc-ILD. There was consensus support amongst rheumatologists (but not pulmonolo­gists) for the use of TCZ in patients with early SSc and ILD with topoisomerase antibodies, worsening condition

|  |  |  |  |
| --- | --- | --- | --- |
| Statement | Mean | SD |  |
| Progression of disease is monitored as follows: |  |  |  |
| Changes in PFTs over time (FVC or DLC0) | 4.56 | 0.58 | ；i ； 4 |
| Features on HRCT (ILD pattern or extent of fibrosis) | 2.80 | 2.43 | i i— |
| Changes in HRCT over time | 4.28 | 0.79 | i « ；十 |
| Changes in symptoms over time | 3.28 | 1.99 |  |
| Exertional hypoxia | 2.64 | 1.96 | \ n— |
| Criteria in defining success in treating SSc-ILD include: |  |  |  |
| FVC stabilization | 3.76 | 0.88 |  |
| FVC improvement | 4.72 | 0.46 |  |
| DLC0 stabilization | 3.68 | 0.85 | ；1 + |
| DLC0 improvement | 4.60 | 0.58 | \ \ \ 4 |
| HRCT improvement | 4.60 | 0.65 | i i i 4 |
| HRCT stabilization | 3.96 | 0.84 |  |
| Symptom stabilization/improvement | 4.12 | 0.83 | *\ \ \ +* |
| 6MWD stabilization/improvement | 2.92 | 1.71 | \ \ -4|— |
| O2 saturation with exercise | 3.00 | 1.26 | i i -1- |
| Functional status (NYHA FC or CPET) | 2.52 | 1.90 | 1 - |

-5.0 -2.5 0.0 2.5 5.0

Mean Delphi score

**Disagree ◄ ► Agree**

**Fig. 6** Consensus recommendations for monitoring progression and defining treatment success in SSc-ILD. *6MWD* 6-min walk distance;

*CPET* cardiopulmonary exercise testing, *DLC0* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *NYHA FC* New York Heart Association Functional Classification, *PFT*pulmonary function test, *SD* standard deviation, *SSc-ILD* systemic sclerosis-associated ILD

defined as deteriorating symptoms and ILD on HRCT and PFTs, and those unable to continue CYC, MMF, or antifibrotics due to adverse effects or lack of achievement with the effective dose.

In cases of progression or worsening of ILD, pulmo­nologists did not achieve consensus on switching to or adding another agent; rheumatologists agreed with both strategies. Regarding weaning, rheumatologists achieved consensus for doing so in cases of lack of efficacy and against stopping therapy quickly; pulmonologists did not achieve consensus on either point.

Discussion

This Delphi study was initiated to develop consensus recommendations for screening, treatment criteria, and the potential role of antifibrotic drugs in patients with SSc-ILD, building on the latest EULAR scleroderma treatment guidelines and the European consensus state­ment [[12](#bookmark105), [14](#bookmark109)]. The relatively low percentage of state­ments reaching consensus is reflective of the uncertainty amongst physicians on the appropriate management of SSc-ILD. Nevertheless, the findings from this study

**Table 2** Notable differences in ratings between specialties

|  |  |
| --- | --- |
| **Statements Rheumatologists** | **Pulmonologists** |
| Which of the following would you likely perform to screen the general scleroderma population for ILD?  6MWD 1.31 (2.69)  When deciding whether to treat patients for ILD do you consider  Potential contribution of reflux? 1.92 (1.71)  In deciding to initiate treatment for SSc-ILD, how important are other parameters besides HRCT and PFTs?  6MWD 1.39 (1.94)  “At initial presentation in patients with SSc, this condition would cause me enough concern about near-term | 2.83 (2.21)  3.17 (1.19)  2.67 (1.50) |
| ILD that I would start treatment right away"  FVC and/or DLC0 < LLN 3.15 (1.52)  What initial therapy do you use once you have decided to treat SSc-ILD?  Methotrexate -3.31 (2.50)  What is your typical/target dose for MMF?  2000 mg daily 3.08 (0.95)  What is your typical/target dose for rituximab?  1 g on days 0 and 15 3.69 (1.70)  I do not utilize rituximab -3.31 (2.36)  Use of antifibrotic drugs  *I see antifibrotic drugs fitting into the management of SSc-ILD after TCZ\* 2.73 (1.56)*  Use of nintedanib [following publication of SENSCIS and INBUILD trial results]  Based on lack of effective response or improvement with immunosuppressive agents (MMF/CYC/*TCZ*) as 1.21 (1.89)  defined by lack of improvement of lung function *2.09 (2.26)\**  Any patient with CTD with clinically significant or worsening ILD 1.64 (1.91)  *1.45 (1.97)\**  Based on lack of effective response or improvement with immunosuppressive agents (MMF/CYC/*TCZ*) as 2.14 (1.92)  defined by a combination of no improvement in symptoms; ILD on HRCT; and/or PFTs *2.55 (2.46)\**  *Nintedanib fits into the management of SSc-ILD as add-on therapy to TCZ\* 2.64 (1.75)*  *Use of TCZ [following publication of focuSSced trial results]\**  *Patients with early SSc and ILD with anti-topoisomerase antibodies 2.55 (0.93)*  *Based on active worsening of patient condition as defined by a combination of worsening symptoms; ILD on HRCT; 2.73 (1.95) and lung function*  *Based on inability to continue CYC/MMF/antifibrotics due to adverse effects 2.91 (0.94)*  *Based on inability to continue CYC/MMF/antifibrotics due to lack of achievement of effective dose with CYC/MMF/ 2.82 (1.40) antifibrotics*  Based on the following response to SSc-ILD treatment, please indicate your likely course of action:  With progression/worsening of ILD, I would switch to another agent 3.77 (1.01)  With progression/worsening of ILD, I would add another agent 3.46 (2.15)  What circumstances would prompt you to consider weaning a patient from therapy?  Lack of efficacy 4.23 (1.17)  How do you wean patients from therapy?  Stop therapy quickly (over weeks or “cold turkey") -4.08 (1.19)  What is success to you?  6MWD stabilization/improvement 2.46 (2.11) | 2.25 (2.22)  -2.33 (2.46)  2.25 (2.42)  0.17 (2.82)  -2.17 (3.01)   1. *(2.33)*   2.45 (1.37)  *3.00 (0.63)\**  2.36 (1.69)  *2.82 (1.25)\**  3.00 (1.41)  *3.55 (0.69)\**  *1.73 (2.69)*  *2.36 (1.12)*  *2.00 (2.49)*   1. *(2.65)*   *2.09 (2.81)*   1. (3.58)   2.33 (3.11)  2.08 (2.64)  -2.42 (3.26)   1. (1.00) |

Results are mean (standard deviation)

*6MWD* 6-min walk distance, *CTD* connective tissue disease, *CYC* cyclophosphamide, *Dg。*diffusing capacity of the lungs for carbon monoxide, *FVC*forced vital capacity, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *LLN* lower limit of normal, *MMF* mycophenolate mofetil, *PFT* pulmonary function test, *SSc* systemic sclerosis, *TCZ* tocilizumab

\*Data from the 2022 supplementary Delphi

provide an algorithm to support effective management of ILD in patients with SSc (Fig. [7](#bookmark74)), currently the leading cause of death in this population [[7](#bookmark96), [8](#bookmark98)].

The expert panelists strongly concurred with the rec­ommendations by the British Society for Rheumatology/ British Health Professionals in Rheumatology endorsing



* Chest auscultation for crackles
* PFTs including spirometry with DLC0
* HRCT chest scans
* Enquire about respiratory symptoms
* Routinely screen for PH and when shortness of breath is not explained by progression of ILD
* FVC <80% and any degree of ILD or symptoms
* >20% total lung involvement on HRCT
* >10% total lung involvement on HRCT with abnormal PFTs
* High-risk patients (early diffuse cutaneous disease) with evidence of mild ILD (<10%)
* Worsening HRCT with symptoms or declining PFTs

, May consider exertional desaturation on SpO2

* Initiate therapy with MMF at 2000-3000 mg/day
* Consider nintedanib for add-on therapy to MMF/CYC
* Use nintedanib in advancing, agressive or progressive ILD/ following failure of immunosupressive therapy
* Initiate nintedanib monotherapy in patients with longstanding ILD where immunosuppressive therapy is not recommended
* Consider TCZ for patients with early SSc-ILD with elevated acute-phase reactants and for those unable to continue CYC/MMF/antifibrotics due to adverse effects
* Follow up with: changes in PFTs (FVC or DLC0) and symptoms over time, features on HRCT and changes in HRCT over time, status of exertional hypoxia
* Success defined as stabilization or improvement of FVC, DLC0, HRCT chest scans, 6MWD, symptoms, and/or O2 saturation with exercise
* Consider tapering/weaning therapy after stability of disease for >2 years

**Fig. 7** Summary of the consensus recommendations for the management of patients with SSc-ILD. *6MWD*6-min walk distance,

*CYC* cyclophosphamide, *DLC0* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *MMF* mycophenolate mofetil, *PFT*pulmonary function test, *PH* pulmonary hypertension, *SpO?* peripheral capillary oxygen saturation, *SSc-ILD* systemic sclerosis-associated ILD, *TCZ*tocilizumab

ILD screening in all SSc patients [[31](#bookmark141)]. The screening tests recommended through this Delphi process are aligned with published studies defining ILD screening criteria in the general SSc population [[1](#bookmark82), [4](#bookmark91)]. However, although HRCT is considered the gold standard for detection of ILD, only 50% of general rheumatologists and 66% of SSc expert rheumatologists order it routinely in newly diagnosed SSc patients, with substantial global practice variation [[32](#bookmark144)].

As well as acknowledging their significance when deciding whether to treat a patient, the panel identified critical thresholds for HRCT, FVC, PFTs, and desatura­tion on exercise. It is important to note that SpO**2** should be measured using detection methods such as fore­head or ear sensors instead of finger sensors, to avoid

misinterpretation resulting from the high prevalence of Raynaud's phenomenon in this population [[33](#bookmark146)]. Despite the lack of supporting literature, since most randomized controlled trials in SSc-ILD exclude such patients, the panel recommended treating ILD in patients with co­existing PH. Rheumatologists placed more value on autoantibody profiles as a prognostic marker than did pulmonologists, which may reflect differences in famili­arity with such biomarkers given the autoimmune nature of many rheumatic conditions. Patients with dcSSc or anti-Scl-70/anti-topoisomerase I antibodies are at higher risk for the development of ILD, whereas patients with limited cutaneous SSc or anti-centromere antibodies are less prone to developing ILD [[13](#bookmark107)]. Consensus was achieved that patients with autoantibodies other than U1 RNP or no specific antibodies should be considered individually to determine the aggressiveness of their dis­ease. There was also consensus that patients with early, rapidly progressive diffuse SSc with mild abnormalities on HRCT and/or PFT would warrant enough concern to support initiating treatment. A broad spectrum of patient characteristics was reviewed when considering who should not be treated for SSc-ILD, with only stable, long­standing disease achieving consensus.

The 2016 EULAR guidelines recommend intravenous CYC for the treatment of SSc-ILD [[14](#bookmark109)]; however, poten­tial toxicity associated with the long-term use of CYC has led to the evaluation of MMF as an alternative. The pan­el's near-unanimous endorsement of MMF (with a target of 2000-3000 mg daily) as first-line therapy is supported by the results from the Scleroderma Lung Study II, in which MMF showed a superior safety profile with com­parable efficacy to CYC [[20](#bookmark118)]. These results also justify the lack of consensus for the use of CYC as an initial therapy.

Nintedanib (150 mg twice daily) has been approved for the management of patients with SSc-ILD based on results from the SENSCIS trial, which reported a 44% reduction in the annual rate of decline in FVC (the pri­mary endpoint) with nintedanib compared with placebo (P = 0.04) [[24](#bookmark127)]. Following the INBUILD trial, it has also been approved for the treatment of patients with chronic fibrosing ILDs with a progressive phenotype, defined as either an FVC decline of > 10% predicted, or worsening respiratory symptoms and an increased extent of fibro­sis on HRCT with or without an FVC decline of 5-10% predicted. The trial demonstrated a 57% reduction in the annual rate of FVC decline with nintedanib compared with placebo (P < 0.001) [[25](#bookmark129)]. Currently, nintedanib is the only antifibrotic drug approved for both indications. In SSc-ILD, the panelists agreed that nintedanib should be considered as add-on therapy to MMF, CYC, or TCZ in patients with advancing or progressive ILD, and after failure of immunosuppressive therapy. In patients with longstanding ILD or in whom immunosuppressive ther­apy is not recommended or not tolerated, nintedanib may be initiated as monotherapy.

TCZ (162 mg every week) is also approved for the man­agement of pulmonary function decline associated with SSc-ILD. This was based on the results of the focuSSced trial, a multicenter, double-blind, placebo-controlled, phase 3 trial that randomized 210 adults with dcSSc for < 60 months and an mRSS of 10-35 to receive sub­cutaneous TCZ 162 mg or placebo weekly for 48 weeks in a 1:1 ratio. Although the trial failed to demonstrate a difference in the primary endpoint of mRSS between the groups (P = 0.10), the secondary analysis of FVC and the exploratory analysis of radiographically determined lung fibrosis suggest that TCZ may have the potential to pre­serve lung function in patients with early diffuse SSc-ILD and elevated acute-phase reactants [[29](#bookmark137)]. There was very little consensus on the use of TCZ as a therapeutic option for patients with SSc-ILD, with greater consensus agree­ment amongst rheumatologists compared with pulmo­nologists. This suggests that, since its approval in 2021, pulmonologists are less comfortable than rheumatolo­gists with using TCZ to treat patients with SSc-ILD.

Pirfenidone has been approved for use in patients with IPF, but not in other progressive fibrotic ILDs [[34](#bookmark148)]. The RELIEF trial, a double-blinded, placebo-controlled, pro­spective phase 2b trial of pirfenidone (2403 mg every day) in patients with fibrotic ILDs other than IPF, was terminated due to futility. However, the results suggest a treatment benefit for patients whose condition dete­riorates despite conventional therapy, based on a slower decline of FVC% predicted from baseline compared with placebo [[27](#bookmark133)]. In addition, a trial evaluating the use of pir- fenidone in combination with MMF in active and symp­tomatic SSc-ILD patients is ongoing [[28](#bookmark135)]. These results may further shift our understanding of how antifibrotic drugs can be more appropriately used in the treatment of patients with SSc-ILD.

Predicting the course of SSc-ILD and defining thera­peutic goals remain challenging. Panelists agreed that stabilization, as well as improvement, in the signs and symptoms of ILD were indicative of treatment success. Recently, new American Thoracic Society guidelines have placed SSc-ILD within a subgroup of ILDs other than IPF which can manifest progressive pulmonary fibrosis, defining progression as a combination of at least two signs based on symptomological, radiological and physio­logical findings [[35](#bookmark150)]. For this Delphi, the panel considered changes in FVC, DL**CO**, HRCT, and symptoms over time as key indicators of disease progression, broadly aligned with this guidance as well as previously published reports [[1](#bookmark82), [4](#bookmark91), [25](#bookmark129), [35](#bookmark150)]. The panel was unable to arrive at a consen­sus on treatment duration. However, they agreed on the conditions under which patients should be weaned off therapy, including weaning over 1-2 years while con­ducting PFTs every 6 months.

The differences in responses between rheumatologists and pulmonologists tended to reflect practice familiarity. The 6MWD is regularly used in pulmonology, while the use of methotrexate and rituximab is more common in rheumatologic conditions. Data comparing intravenous rituximab with monthly pulses of CYC support the rheu­matologists' recommendation on this point [[36](#bookmark152)]. These differences highlight the importance of multidisciplinary management of SSc-ILD, combining expertise across the multifaceted clinical manifestations of SSc.

There are limitations embedded in the Delphi process. There are no standard criteria defining consensus in Del­phi studies, and given the breadth of topics investigated with this method, such standardization may not be feasi­ble. Designed to elicit guidance when no strong evidence is available, the process is not statistically rigorous, and when consensus is reached there is no guarantee that it is generalizable or appropriate. Bias may be introduced during panel selection and development of the initial questionnaire. Anonymity, an integral component of the Delphi process, devolves panelists from accountability for their responses, with the consequence that these may be based on insufficient or minimal consideration. Equal weighting of responses means panelists with relatively less experience may have an impact on consensus dispro­portionate to their familiarity with the subject matter. In this study, limiting the expert panel to 25 participants to ensure a manageable process may have resulted in miss­ing important perspectives from a larger, more represent­ative population of physicians. Restricting participation to those practicing in the US focused recommendations on those relevant to and feasible within that locale, but limited the capture of global perspectives. Not including patients, pharmacists, payers, and other potential stake­holders (such as physicians practicing in the community) in the panel may have impacted the diversity of opinions and alignment of these recommendations with the Insti­tute for Healthcare Improvement Triple Aim Initiative [[37](#bookmark154)].

Conclusions

This modified Delphi study involving experts in pulmo­nology and rheumatology facilitated the development of consensus recommendations and a management algo­rithm for screening, treatment criteria, and the potential role of antifibrotics and TCZ in patients with SSc-ILD in a real-world setting. Pulmonologists and rheumatologists aligned for the majority of recommendations, with some subtle differences in their perspectives on treatment ini­tiation and therapeutic approaches. These differences highlight the importance of collaborative management of patients and the clinical impact of multidisciplinary discussion groups. Findings from this study provide a management algorithm that will be critical for treat­ing patients with SSc-ILD and help expand on the latest guidelines with clinical expertise and consideration of recently published trials in SSc-ILD.

**Abbreviations**

6MWD 6-Minute walk distance

CYC Cyclophosphamide

dcSSc Diffuse cutaneous SSc

DLco Diffusing capacity of the lungs for carbon monoxide

EULAR European League Against Rheumatism

FVC Forced vital capacity

HRCT High-resolution computed tomography

ILD Interstitial lung disease

IPF Idiopathic pulmonary fibrosis

MMF Mycophenolate mofetil

mRSS Modified Rodnan skin score

PFT Pulmonary function test

PH Pulmonary hypertension

SD Standard deviation

SpO? Peripheral capillary oxygen desaturation

SSc Systemic sclerosis

TCZ Tocilizumab

**Supplementary Information**

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**Additional file 1. Table S1.** SSc-ILD Delphi Questionnaire 3 results. **Table S2.** SSc-ILD Delphi Supplemental Questionnaire 2 results

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**Author contributions**

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part thereof are appropri­ately investigated and resolved. FFR and DK made substantial contributions to the conception and design of the work. FFR, DK, VMH, RJK, MDM, IOR, RS, VDS, MES and RTD were members of the Delphi advisory board and contributed to panel selection and development of Delphi Questionnaire 1. All authors participated in at least two surveys including the final survey. All authors contributed to the interpretation of the data, and to drafting and revising the manuscript. All authors read and approved the final manuscript. The view­points expressed in this manuscript solely represent those of its authors.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

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References

1. Denton CP Khanna D. Systemic sclerosis. Lancet. 2017;390:1685-99.
2. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009;360:1989-2003.
3. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest. 2007;117:557-67.
4. Silver KC, Silver RM. Management of systemic-sclerosis-associated intersti­tial lung disease. Rheum Dis Clin North Am. 2015;41:439-57.
5. Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. Eur Respir Rev. 2013;22:6-19.
6. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, Tan FK, Zhou X, Ahn C, Feghali-Bostwick CA, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemo­graphic, and behavioral factors. Arthritis Rheum. 2007;57:318-26.
7. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007;66:940-4.
8. Tyndall AJ, Bannert B, Vonk M, Airo P Cozzi F, Carreira PE, Bancel DF, Allanore Y, Muller-Ladner U, Distler O, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69:1809-15.
9. Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, Garen T, Salberg A, Brunborg C, Midtvedt O, et al. Tracking impact of inter­stitial lung disease in systemic sclerosis in a complete nationwide cohort. Am J Respir Crit Care Med. 2019;200:1258-66.
10. Bergamasco A, Hartmann N, Wallace L, Verpillat P Epidemiology of sys­temic sclerosis and systemic sclerosis-associated interstitial lung disease. Clin Epidemiol. 2019;11:257-73.
11. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res. 2019;20:13.
12. Hoffmann-Vold A-M, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, Bruni C, Carducci P Carreira PE, Castellvi I, et al. The identifica­tion and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatology. 2020;2:e71-83.
13. Schoenfeld SR, Castelino FV. Interstitial lung disease in scleroderma. Rheum Dis Clin North Am. 2015;41:237-48.
14. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, Distler O, Clements P Cutolo M, Czirjak L, et al. Update of EULAR recom­mendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76:1327-39.
15. Kowal-Bielecka O, Landewe R, Avouac J, Chwiesko S, Miniati I, Czirjak L, Clements P Denton C, Farge D, Fligelstone K, et al. EULAR recom­mendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis. 2009;68:620-8.
16. Khanna D, Lescoat A, Roofeh D, Bernstein EJ, Kazerooni EA, Roth MD, Martinez F, Flaherty KR, Denton CP. Systemic sclerosis-associated inter­stitial lung disease: how to incorporate two Food and Drug Admin­istration-approved therapies in clinical practice. Arthritis Rheumatol. 2022;74:13-27.
17. Panopoulos ST, Bournia VK, Trakada G, Giavri I, Kostopoulos C, Sfikakis PP. Mycophenolate versus cyclophosphamide for progressive interstitial lung disease associated with systemic sclerosis: a 2-year case control study. Lung. 2013;191:483-9.
18. Volkmann ER, Tashkin DF, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, Kim G, Goldin J, Clements PJ, Furst DE, Elashoff RM. Mycophenolate mofetil versus placebo for systemic sclerosis-related interstitial lung disease: an analysis of Scleroderma Lung Studies I and II. Arthritis Rheu­matol. 2017;69:1451-60.
19. Gerbino AJ, Goss CH, Molitor JA. Effect of mycophenolate mofetil on pulmonary function in scleroderma-associated interstitial lung disease. Chest. 2008;133:455-60.
20. Tashkin Dp Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, Goldin

J, Arriola E, Volkmann ER, Kafaja S, 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;4:708-19.

1. Tashkin Dp Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, Arriola E, Silver R, Strange C, Bolster M, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354:2655-66.
2. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, Lederer DJ, Mulligan MJ, Patterson GA, Singer LG, et al. A consensus document for the selection of lung transplant candidates: 2014-an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34:1-15.
3. Bernstein EJ, Peterson ER, Sell JL, D'Ovidio F, Arcasoy SM, Bathon JM, Lederer DJ. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. Arthritis Rheumatol. 2015;67:1314-22.
4. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, Raghu G, Sauter W, Girard M, Alves M, et al. Nintedanib for systemic scle­rosis-associated interstitial lung disease. N Engl J Med. 2019;380:2518-28.
5. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzla 仟 K, Stowasser S, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381:1718-27.
6. OFEV® (nintedanib): prescribing information. [https://www.accessdata.fda.](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205832s014lbl.pdf) [gov/drugsatfda\_docs/label/2020/205832s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205832s014lbl.pdf)
7. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, Bonnet R, Grohe C, Held M, Wilkens H, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021;9:476-86.
8. Scleroderma Lung Study III一combining pirfenidone with mycopheno- late (SLSIII)<https://clinicaltrials.gov/ct2/show/NCT03221257>
9. Khanna D, Lin CJF, Furst DE, Goldin J, Kim G, Kuwana M, Allanore Y, Matucci-Cerinic M, Distler O, Shima Y, et al. Tocilizumab in systemic sclero­sis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2020;8:963-74.
10. ACTEMRA (tocilizumab): prescribing information. [https://www.acces](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf) [sdata.fda.gov/drugsatfda\_docs/label/2021/125276s131lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf)
11. Denton CP, Hughes M, Gak N, Vila J, Buch MH, Chakravarty K, Fligelstone

K, Gompels LL, Griffiths B, Herrick AL, et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology (Oxford). 2016;55:1906-10.

1. Bernstein EJ, Khanna D, Lederer DJ. Screening High-Resolution Com­puted Tomography of the Chest to Detect Interstitial Lung Disease in Sys­temic Sclerosis: A Global Survey of Rheumatologists. Arthritis Rheumatol. 2018;70:971-2.
2. Wilsher M, Good N, Hopkins R, Young P, Milne D, Gibson A, Suppiah R, Ly J, Doughty R, Dalbeth N. The six-minute walk test using forehead oximetry is reliable in the assessment of scleroderma lung disease. Respirology. 2012;17:647-52.
3. ESBRIET® (pirfenidone): prescribing information [[https://www.accessdata.](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022535s012,208780s002lbl.pdf) [fda.gov/drugsatfda\_docs/label/2019/022535s012,208780s002lbl.pdf]](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022535s012,208780s002lbl.pdf)
4. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM, Martinez FJ, 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:e18-47.
5. Sircar G, Goswami RP, Sircar D, Ghosh A, Ghosh P. Intravenous cyclophos­phamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. Rheumatology (Oxford). 2018;57:2106-13.
6. IHI Triple Aim Initiative [[http://www.ihi.org/engage/initiatives/TripleAim/](http://www.ihi.org/engage/initiatives/TripleAim/Pages/default.aspx) [Pages/default.aspx](http://www.ihi.org/engage/initiatives/TripleAim/Pages/default.aspx)]. Accessed 8 June 2021.

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