The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements

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Summary

Background Systemic sclerosis-associated interstitial lung disease (ILD) carries a high mortality risk; expert guidance is required to aid early recognition and treatment. We aimed to develop the first expert consensus and define an algorithm for the identification and management of the condition through application of well established methods.

Methods Evidence-based consensus statements for systemic sclerosis-associated ILD management were established for six domains (ie, risk factors, screening, diagnosis and severity assessment, treatment initiation and options, disease progression, and treatment escalation) using a modified Delphi process based on a systematic literature analysis. A panel of 27 Europe-based pulmonologists, rheumatologists, and internists with expertise in systemic sclerosis-associated ILD participated in three rounds of online surveys, a face-to-face discussion, and a WebEx meeting, followed by two supplemental Delphi rounds, to establish consensus and define a management algorithm. Consensus was considered achieved if at least 80% of panellists indicated agreement or disagreement.

Findings Between July 1, 2018, and Aug 27, 2019, consensus agreement was reached for 52 primary statements and six supplemental statements across six domains of management, and an algorithm was defined for clinical practice use. The agreed statements most important for clinical use included: all patients with systemic sclerosis should be screened for systemic sclerosis-associated ILD using high-resolution CT; high-resolution CT is the primary tool for diagnosing ILD in systemic sclerosis; pulmonary function tests support screening and diagnosis; systemic sclerosis-associated ILD severity should be measured with more than one indicator; it is appropriate to treat all severe cases; no pharmacological treatment is an option for some patients; follow-up assessments enable identification of disease progression; progression pace, alongside disease severity, drives decisions to escalate treatment.

Interpretation Through a robust modified Delphi process developed by a diverse panel of experts, the first evidence-based consensus statements were established on guidance for the identification and medical management of systemic sclerosis-associated ILD.

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Introduction

Patients with systemic sclerosis are at high risk of developing interstitial lung disease (ILD). 50% of patients with systemic sclerosis have ILD when first assessed by high-resolution CT (HRCT),[1] although a lesser proportion of patients have a severe reduction in pulmonary function.[2] Early diagnosis, severity assessment, prediction of progression, and appropriate treatment of systemic sclerosis-associated ILD is necessary to achieve the best possible patient outcomes.[3] However, differences in screening approaches, few treatment options, and an absence of consensus guidelines make effective, early intervention difficult in clinical practice.

Treatment recommendations for the management of systemic sclerosis were updated in 2016 by the European League Against Rheumatism/European Scleroderma Trial and Research group,[4] and treatment algorithms for systemic sclerosis were published in 2018 by the Scleroderma Algorithm Group.[5] In 2019, a consensus was established on strongly suggested tools for a minimum annual systemic assessment of organ involvement in systemic sclerosis.[6] Although these recommendations offer important clinical treatment guidance for systemic sclerosis, statements regarding the specific management of systemic sclerosis-associated ILD are limited to recommendations regarding treatment with cyclophosphamide[4,7] or mycophenolate mofetil,[5] and multidisciplinary consensus is highly in demand to guide the clinical management of this complex patient group.[8] Ideally, such guidance would include detailed evidence-based statements on

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Research in context

Evidence before this study

Patients with systemic sclerosis are at high risk of developing interstitial lung disease (ILD), but guidance is scarce regarding the specific management of systemic sclerosis-associated ILD. Although clinical guidance for systemic sclerosis-associated ILD has been published in review articles previously, to our knowledge there are no existing recommendations using well established consensus methods. We did a systematic search of the literature from Jan 01, 2012, to April 30, 2018, including grey literature (searched between 1992 and 2011), using multiple electronic databases. Guidelines, meta-analyses, randomised controlled trials, and observational studies reporting on risk stratification, screening, diagnosis, treatment, and management outcomes for patients with systemic sclerosis-associated ILD were included.

Added value of this study

This study provides the first evidence-based expert consensus statements for systemic sclerosis-associated ILD management across six key domains—risk factors, screening, diagnosis and severity assessment, treatment initiation and options, disease progression, and treatment escalation—and an systemic sclerosis-associated ILD management algorithm for use in clinical practice using well established consensus methods.

Implications of all the available evidence

These evidence-based expert consensus statements provide important clinical guidance for the early identification and medical management of systemic sclerosis-associated ILD, and offer a framework for future treatment decision making.

screening, diagnosis, treatment, and assessment of disease progression.[9] With the availability of nintedanib as the first US FDA-approved treatment to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated ILD,[10] and further treatments in advanced clinical testing, there is a rapidly increasing need for clinical management algorithms leading to improved morbidity and mortality outcomes. Although clinical guidance for systemic sclerosis-associated ILD has been published previously in review articles,[11,12] there are, to our knowledge, no existing recommendations using well established consensus methods.

We therefore aimed to establish expert consensus statements for systemic sclerosis-associated ILD in six key domains (ie, risk factors, screening, diagnosis and severity assessment, treatment initiation and options, disease progression, and treatment escalation) and to develop a management algorithm providing a framework for future clinical decision making. To meet these objectives, an initial set of statements on systemic sclerosis-associated ILD was developed based on a comprehensive systematic literature review, and evidence-based expert consensus was achieved using a modified Delphi process that included 27 European pulmonologists, rheumatologists, and internists.

Methods

Systematic literature review

We did a systematic literature review,[13] which will be reported in detail separately. Briefly, 280 articles on systemic sclerosis-associated ILD published between Jan 1, 1992, and April 30, 2018, were selected for content extraction and analysis. Extracted information was used to derive evidence-based draft statements for six domains of systemic sclerosis-associated ILD management: (1) risk factors, (2) screening, (3) diagnosis and severity assessment, (4) treatment initiation and options, (5) disease progression, and (6) treatment escalation. The level of supporting evidence was graded as high, moderate, or low.[14] Additional draft statements were included at the suggestion of the steering committee.

Expert panel and steering committee

In March, 2018, Europe-based physicians experienced in the diagnosis and management of systemic sclerosis-associated ILD were recruited as members of the Delphi panel. Candidate experts were identified through an Embase review of recent guidelines from 2016, publications, and conferences related to systemic sclerosis-associated ILD from 2018; those who were affiliated to European Scleroderma Trial and Research registered centres were also identified. The panel was designed to represent the different specialties involved in treating patients with systemic sclerosis-associated ILD and comprised rheumatologists, pulmonologists, and internists. Each panel member was required to have at least 5 years of clinical experience managing patients with systemic sclerosis-associated ILD.

A steering committee of three rheumatologists, two pulmonologists, and a non-clinical chair (experienced in steering committees relating to general practice and specialty medicine) contributed to study planning and development, reviewed survey results, and led scientific discussions. Patients and the public were not involved in the design or conduct of this study.

Modified Delphi process

A modified Delphi process was used to develop expert consensus statements for the diagnosis and management of systemic sclerosis-associated ILD.[15] This method is well established as a robust consensus technique[16] for health-related cases in which clinical evidence might be insufficient or contradictory.[17,18]

Between July 1, and Nov 30, 2018, panellists participated in three rounds of online surveys. At each round, panellists were asked to anonymously indicate their level of

agreement with proposed statements on a scale of 1 (strong disagreement) to 7 (strong agreement). Each statement included links to supporting evidence. Panellists were encouraged to express in writing their responses to the statements. Panel responses were used as the basis for any new or revised statements to be presented in the next round of voting. The steering committee reviewed adapted statements alongside voting results and responses, proposed modifications, and provided input for algorithm development.

The first round assessed panel consensus on 78 statements based on the results of the systematic literature review and clinical experience of the steering committee. The second round included voting on new statements, and on modified versions of statements that had not reached consensus in round one.

Consensus agreement statements from rounds one and two were used to create an initial draft management algorithm for systemic sclerosis-associated ILD, which was then refined by the steering committee before being evaluated during a face-to-face panel discussion. Panellists agreed on any revised statements and the algorithm was defined. A WebEx meeting was held before round three to discuss remaining non-consensus statements, clarify queries identified in rounds one and two, and align on statement understanding.

Non-consensus statements from rounds one and two were put forward for a third round of voting. Any statements that reached consensus at this stage were added to the algorithm and reviewed by the steering committee.

Supplemental Delphi process

As studies with potential systemic sclerosis-associated ILD treatment options (nintedanib[19] and tocilizumab[20]) were published or presented after the primary Delphi process, a supplemental Delphi process was done between July 31, 2019, and Aug 27, 2019, to extend and update the primary findings. 14 statements relating to nintedanib or tocilizumab, or both, were generated by members of the steering committee. These statements were shared with the Delphi panel via email, as an Excel spreadsheet, and voting responses were collected in a further two rounds of online voting. As with the primary Delphi process, panellists were encouraged to express in writing their responses to the statements, and panel responses were used as the basis for any new or revised statements to be presented in the next round of voting.

Statistical analysis

Measures for central tendency and level of dispersion were determined for each statement at each round. For each consensus statement, mean score and SD are reported. Consensus was considered to be achieved when 80% or more of the panel either disagreed (score of 1, 2, or 3) or agreed (score of 5, 6, or 7) with a statement. The influence of medical speciality was assessed with the Mann–Whitney U test.

Role of the funding source

This study was funded by Boehringer Ingelheim International, Germany. The sponsor had no influence on data generation and interpretation in this study. Although the study was funded by Boehringer Ingelheim, the company had no influence on the steering committee discussions and decisions nor the panellists' discussions and voting. The sponsor had no influence on design or implementation of the Delphi process, including selection of the panellists, nor on data generation and interpretation in this study; the concept for the study and study initiation came from the steering committee. The sponsor was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

31 panellists were recruited initially: 19 rheumatologists, eight pulmonologists, and four internists. The panel members were based in Italy (n=6), the UK (n=5), France (n=5), Spain (n=5), Germany (n=4), Czech Republic (n=2), Poland (n=2), Switzerland (n=1), and Austria (n=1). Median systemic sclerosis-associated ILD treatment experience per panellist was 11 years (IQR 8–15). Collectively, panel members had treated more than 1400 patients with systemic sclerosis-associated ILD during the past year. Overall, 27 panellists (87%) completed all rounds of the study: 16 rheumatologists, seven pulmonologists, and four internists.

Across all three rounds of the primary modified Delphi process, 95 statements were tested and consensus was reached on 67 statements (71%): 52 statements reached the threshold for consensus agreement and 15 reached the threshold for consensus disagreement (ie, consensus was reached that participants disagreed with the proposed statement). Medical speciality had no meaningful influence on voting, as analysed by the Mann–Whitney U test.

Statements that reached consensus agreement are presented in table 1 and those that reached consensus disagreement are presented in table 2. The full systemic sclerosis-associated ILD management algorithm, which was finalised following a face-to-face panel discussion during the primary modified Delphi process, is shown in figure 1. In the full algorithm, the six domains of systemic sclerosis-associated ILD management are subdivided into nine sections: risk factors (section 1), screening (section 2), diagnosis and severity assessment (sections 3 and 4), treatment initiation and options (sections 5 and 6), disease progression (section 7), and treatment escalation (sections 8 and 9). The statements likely to have the greatest clinical impact, in the opinion of the steering committee, are described below.

For risk factors, consensus was reached on the following statements: respiratory symptoms, smoking history, ethnicity (Native American; African heritage), male sex,

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	Score	Level of agreement
1: Risk factors		
1.1: Prior and coexisting medical conditions might increase the likelihood of a patient with systemic sclerosis having or developing ILD	5·2 (1·1)	83%
1.2: Respiratory symptoms and smoking history might increase the likelihood of the patient with systemic sclerosis having or developing ILD*	5·3 (1·5)	81%
1.3: Diffuse cutaneous systemic sclerosis and systemic sclerosis sine scleroderma might increase the likelihood of a patient with systemic sclerosis having or developing ILD	5·7 (1·4)	81%
1.4: Ethnicity influences the likelihood of a patient with systemic sclerosis having or developing ILD	5·3 (1·2)	81%
1.5: Gender influences the likelihood of a patient with systemic sclerosis having or developing ILD	5·6 (1·0)	87%
1.6: Laboratory parameters such as anti-centromere and anti-topoisomerase antibodies might increase the likelihood of a patient with systemic sclerosis having or developing ILD	6·1 (1·3)	90%
1.7: The presence of anti-centromere antibodies decreases the likelihood of a patient with systemic sclerosis having or developing ILD	5·2 (1·2)	87%
1.8: The presence of anti-topoisomerase I antibodies increases the likelihood of a patient with systemic sclerosis having or developing ILD	6·5 (0·9)	94%
1.9: Other biomarkers that are described in academic literature (eg, KL-6, serum surfactant protein D [SP-D], CXCL1, miR-200, neutrophil to lymphocyte ratio, ALOX5AP polymorphisms, CCL18, CXCL4, MCP1, CXCR3, CXCR4, IL-10, and PIC) are not commonly used in clinical practice to assess the likelihood of a patient with systemic sclerosis having or developing ILD	6·4 (1·5)	90%
2: Screening		
2.1: Patients with systemic sclerosis should be screened for systemic sclerosis-associated ILD using HRCT, particularly if they are showing one or more risk factors	6·1 (1·6)	84%
2.2: Respiratory symptoms such as frequent cough or dyspnoea could suggest the presence of ILD in patients with systemic sclerosis	6·5 (0·9)	97%
2.3: Lung function testing should be done in patients with systemic sclerosis to provide a baseline parameter for diagnosis	6·9 (0·4)	100%
3: Diagnosis and severity assessment		
3.1: The primary tool to diagnose ILD in patients with systemic sclerosis is HRCT	6·8 (0·4)	100%
3.2: DL_{co} is an effective diagnostic tool to assess the presence of ILD in patients with systemic sclerosis	5·6 (1·4)	84%
3.3: FVC is an effective diagnostic tool to assess the presence of ILD in patients with systemic sclerosis	5·8 (1·3)	81%
3.4: Disease severity can be assessed using lung function	6·4 (1·0)	97%
3.5: Disease severity can be assessed using FVC value	6·2 (0·7)	100%
3.6: Disease severity can be assessed using FVC value variation from baseline	6·2 (1·0)	97%
3.7: Disease severity can be assessed using the percentage predicted FVC value	5·8 (1·2)	94%
3.8: Disease severity can be assessed using DL_{co} value†	5·8 (0·5)	100%
3.9: Disease severity can be assessed using the percentage predicted DL_{co} value	5·6 (1·1)	90%
3.10: Disease severity can be assessed using HRCT fibrosis score	6·1 (1·0)	90%
3.11: Disease severity can be assessed using diffusing capacity for carbon monoxide†	5·5 (1·3)	81%
3.12: Disease severity can be assessed using exercise-induced blood oxygen saturation	5·0 (1·1)	89%
3.13: Systemic sclerosis-associated ILD disease severity has to be measured with more than one indicator	6·5 (0·6)	100%
4: Treatment initiation and options		
4.1: Clinical guidelines drive treatment recommendations‡ in managing patients with systemic sclerosis-associated ILD	5·5 (1·1)	81%
4.2: Clinical experience drives treatment recommendations‡ in managing patients with systemic sclerosis-associated ILD	5·5 (0·9)	87%
4.3: All patients with systemic sclerosis-associated ILD considered as early, stable, or mild need to be followed up closely (every 3–6 months) and treatment initiated in case of progression	6·3 (0·9)	97%
4.4: Decisions to initiate, change, or stop treatment are a combination of the current disease state and the speed of progression	6·4 (0·7)	97%
4.5: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is survival rate	5·8 (1·3)	94%
4.6: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is response rate after previous treatment	5·2 (1·0)	81%
4.7: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is prolongation of time to progression	6·1 (1·0)	94%
4.8: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is speed of improvement of patient's symptoms	5·6 (1·1)	84%

(Table 1 continues on next page)

	Score	Level of agreement
(Continued from previous page)		
4.9: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is safety and tolerability	5·8 (1·0)	90%
4.10: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is quality of life	6·1 (0·8)	100%
4.11: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is previous clinical experience	5·2 (0·9)	83%
4.12: The driver for treatment recommendation‡ in patients with systemic sclerosis-associated ILD is scientific evidence of efficacy	6·5 (0·8)	97%
4.13: No treatment is an option for some patients with systemic sclerosis-associated ILD	5·6 (1·5)	84%
4.14: Mycophenolate mofetil is an effective treatment for patients with systemic sclerosis-associated ILD	6·0 (1·3)	90%
4.15: Cyclophosphamide is an effective treatment for patients with systemic sclerosis-associated ILD	5·7 (1·5)	84%
5: Disease progression		
5.1: The percentage predicted FVC value can indicate disease progression in patients with systemic sclerosis-associated ILD	6·3 (0·8)	100%
5.2: The percentage predicted DL_{co} value is a measure of disease progression in patients with systemic sclerosis-associated ILD	6·0 (0·9)	94%
5.3: FVC at treatment initiation is a measure of disease progression in patients with systemic sclerosis-associated ILD	5·4 (1·3)	84%
5.4: Disease progression in patients with systemic sclerosis-associated ILD can be defined by an FVC decrease threshold	6·0 (1·0)	90%
5.5: DL_{co} at treatment initiation can indicate disease progression in patients with systemic sclerosis-associated ILD	5·4 (1·5)	84%
5.6: Lung function is an effective post-diagnostic long-term follow-up measurement for assessing disease progression in patients with systemic sclerosis-associated ILD	6·6 (0·7)	100%
5.7: Extent of fibrosis is a measure of disease progression in patients with systemic sclerosis-associated ILD	5·9 (1·2)	87%
5.8: The decision to do HRCT is based on a combination of the current disease state and the speed of progression	6·3 (1·1)	97%
5.9: Exercise-induced blood oxygen saturation can indicate disease progression in patients with systemic sclerosis-associated ILD	5·4 (1·1)	85%
6: Treatment escalation		
6.1: Speed of progression, alongside disease severity, drives decisions to escalate treatment	6·7 (0·5)	100%
6.2: Haemopoietic stem-cell transplantation is an effective treatment for a subset of patients with systemic sclerosis-associated ILD	5·2 (0·9)	80%
6.3: Lung transplant is an effective treatment for a subset of patients with systemic sclerosis-associated ILD	5·8 (1·2)	84%

Data are mean (SD) or %. Statements were rated from 1 (strong disagreement) to 7 (strong agreement). ALOX5AP=arachidonate 5-lipoxygenase activating protein. CCL=chemokine (C-C motif) ligand. CXCL=chemokine (C-X-C motif) ligand. CXCR=chemokine (C-X-C motif) receptor. DL_{co}=diffusing capacity of the lungs for carbon monoxide. FVC=forced vital capacity. HRCT=high-resolution CT. ILD=interstitial lung disease. KL-6=Krebs von den Lungen-6. MCP1=monocyte chemoattractant protein 1 (also known as CCL2). miR-200=microRNA-200. PIC=plasma plasmin-α2-plasmin inhibitor complex. *Respiratory symptoms and smoking history as two separate risk factors, not in the same patient. †Statement 3.11 reached consensus in Delphi round one and statement 3.8 reached consensus in Delphi round two; as the wording of statements was adapted (for subsequent voting of statements that did not reach consensus), based on panel feedback during the initial voting rounds, these two statements have been voted on and reached consensus twice (in error because wording was misleading). ‡Driver for treatment recommendation refers to the driver for the treatment choice that is recommended to individual patients.

Table 1: **Expert consensus agreement statements on systemic sclerosis-associated ILD (primary Delphi process)**

and the presence of diffuse cutaneous systemic sclerosis increase the risk of ILD in patients with systemic sclerosis.[21–26] The presence of anti-topoisomerase I antibodies also increases the likelihood of a patient with systemic sclerosis having or developing ILD, whereas the presence of anti-centromere antibodies decreases the likelihood.[25,27,28] It is noteworthy that the statement "diffuse cutaneous systemic sclerosis and systemic sclerosis sine scleroderma may increase the likelihood of an systemic sclerosis patient having or developing ILD" only just reached consensus agreement (81%). Indeed, some panellists responded during voting that there was a common view that only diffuse cutaneous systemic sclerosis increases risk for ILD, and that the risk with systemic sclerosis sine scleroderma is similar to that of limited cutaneous systemic sclerosis; this view was reflected in broader panel discussion at the face-to-face meeting before development of the algorithm. Although other biomarkers (such as Krebs von den Lungen-6 and surfactant protein D) have been reportedly associated with systemic sclerosis-associated ILD,[29,30] there was consensus agreement that these are not commonly used in clinical practice.

For screening, there was consensus that all patients with systemic sclerosis should be screened at baseline for ILD using HRCT,[31–33] with pulmonary function testing (forced vital capacity [FVC] and diffusing capacity of carbon monoxide [DL_{CO}]) to provide baseline parameters, and auscultation.[33–36] Screening with pulmonary function tests should be repeated regularly in all patients with systemic sclerosis.[12,33–35] There were no consensus statements regarding HRCT screening intervals. The frequency of screening and use of HRCT should be determined by the clinician, guided by the risk of an individual developing ILD.[25,32,37,38] Panel feedback during

	Score	Level of agreement
1: Risk factors		
1.1: Women with systemic sclerosis are more likely to develop ILD	2·6 (1·3)	80%
1.2: Pulmonary artery hypertension might consistently increase the likelihood of a patient with systemic sclerosis having or developing ILD	2·2 (1·1)	93%
2: Screening		
2.1: Associated Raynaud's phenomena might suggest the presence of ILD in patients with systemic sclerosis	1·7 (1·1)	93%
3: Diagnosis and severity assessment		
3.1: Serial cardiopulmonary exercise testing is an effective tool for assessing the presence of ILD in patients with systemic sclerosis	2·6 (1·3)	81%
3.2: Exhaled nitric oxide is an effective diagnostic tool for assessing the presence of ILD in patients with systemic sclerosis	2·5 (1·2)	89%
3.3: Disease severity can be assessed using the pulmonary artery to ascending aorta ratio	2·5 (1·2)	85%
3.4: Disease severity can be assessed using exhaled nitric oxide	2·4 (1·0)	93%
3.5: Disease severity can be assessed using frequency of cough	2·4 (1·0)	90%
3.6: Disease severity can be assessed using right ventricular systolic pressure	2·5 (1·2)	85%
3.7: Disease severity can be assessed using oesophageal diameter	2·4 (1·2)	89%
4: Treatment initiation and options		
4.1: Glucocorticoids are an effective treatment for patients with systemic sclerosis-associated ILD	2·8 (1·0)	80%
5: Disease progression		
5.1: Patients with systemic sclerosis-associated ILD should undergo HRCT assessment annually	2·5 (1·5)	81%
5.2: The pulmonary artery to ascending aorta ratio is a measure of disease progression in patients with systemic sclerosis-associated ILD	2·4 (1·3)	93%
5.3: Arthritis can indicate disease progression in patients with systemic sclerosis-associated ILD	2·4 (1·2)	83%
5.4: Oesophageal diameter can indicate disease progression in patients with systemic sclerosis-associated ILD	2·7 (1·1)	85%
6: Treatment escalation		
No consensus disagreement statements	..	..

Data are mean (SD) or %. Statements were rated from 1 (strong disagreement) to 7 (strong agreement). Consensus disagreement statements are statements to which the majority (≥80%) of participants disagreed. The level of agreement reflects the proportion of panellists voting that the statement is not true. HRCT=high-resolution CT. ILD=interstitial lung disease.

Table 2: **Expert consensus disagreement statements on systemic sclerosis-associated ILD (primary Delphi process)**

the voting round suggested that abnormalities on x-ray or pulmonary function testing and presence of dyspnoea warranted the use of HRCT. During discussion, some panellists noted that it was important to avoid the overuse of HRCT, given the potentially unnecessary risk of radiation exposure, particularly in those patients with stable disease. However, HRCT techniques have advanced considerably in recent years and modern scanners use lower doses of radiation to achieve higher quality scans so that the accumulated radiation dose of a single, high-quality HRCT examination is now typically 1·5–2·5 mSv.[39] In addition, low dose HRCT protocols have been validated in systemic sclerosis-associated ILD.[40] The threshold for consensus was not reached (agreement level 74%) on whether the presence of oesophageal dilation (as a surrogate marker for reflux disease) could increase the likelihood of a patient with systemic sclerosis having or developing ILD.[41,42] However, some panellists commented during the voting rounds that aspiration associated with oesophageal dilation might be involved in the development of ILD.

For diagnosis and severity assessment, agreement was reached that the primary tool for diagnosing ILD in patients with systemic sclerosis is HRCT, with pulmonary function tests (FVC and DL_{CO}), and clinical assessment of respiratory symptoms as supporting diagnostic tools.[12,43] Severity of ILD in patients with systemic sclerosis can be assessed using HRCT pattern and extent.[44] However, more than one measure should be used to determine severity: respiratory symptoms such as dyspnoea (with or without 6-min walk test) should be considered, as well as exercise-induced oxygen desaturation and quality of life.[38,45] There was consensus disagreement regarding the use of exhaled nitric oxide to diagnose ILD and to assess severity, as well as cough frequency and oesophageal diameter as measures of ILD severity.[42,46–48] Consensus was not reached on the effectiveness of lung ultrasound in diagnosing ILD in patients with systemic sclerosis, although this technique has been the subject of recent research.[49–51]

For treatment initiation and options, in the opinion of the experts, multiple factors are drivers of treatment initiation and assessment of appropriate options for an

Figure 1: **Detailed management algorithm for systemic sclerosis-associated ILD**
Statements are based on evidence published up until April 30, 2018. ILD=interstitial lung disease. FVC=forced vital capacity. HRCT=high-resolution CT. DL_{CO}=diffusing capacity of the lungs for carbon monoxide.

1. Risk factors that can be considered in patients with systemic sclerosis to be indicative of developing ILD

- The presence of anti-topoisomerase I antibodies increases the likelihood of a patient with systemic sclerosis having or developing ILD
- The presence of anti-centromere antibodies decreases the likelihood of a patient with systemic sclerosis having or developing ILD
- Diffuse cutaneous systemic sclerosis
- Respiratory symptoms
- Ethnicity
- Native American and of African heritage
- Male individuals are at higher risk

2. Which patients should be screened, with what method and frequency

Symptoms

- Respiratory symptoms such as frequent cough or dyspnoea might suggest the presence of ILD in patients with systemic sclerosis

Tools

- All patients with systemic sclerosis should be screened for ILD
- Lung function testing (FVC and diffusion capacity) should be done in patients with systemic sclerosis to provide a baseline parameter
- Lung function testing (FVC and diffusion capacity) should be repeated regularly as screening in all patients with systemic sclerosis
- Every patient should receive an auscultation
- All patients with systemic sclerosis should be screened at baseline with HRCT
- Frequency of screening should be guided by likelihood of developing ILD combined with symptoms
- Using HRCT should be guided by likelihood of developing ILD combined with symptoms and lung function

3. Diagnostic tools that should be used to identify the presence of ILD in patients with systemic sclerosis and criteria for using each

- The primary tool to diagnose ILD in patients with systemic sclerosis is HRCT
- DL_{CO} is a supporting tool for diagnosing ILD in patients with systemic sclerosis
- FVC is a supporting tool for diagnosing ILD in patients with systemic sclerosis
- Assessment of clinical symptoms is a supporting tool for diagnosing ILD in patients with systemic sclerosis

4. Tools to diagnose severity of disease

Diagnosis tools for severity

Needs to be measured with more than one tool

- HRCT pattern and extent
- Lung function
- FVC value
- Percentage predicted FVC value
- Disease severity can be assessed using FVC value variation from baseline
- DL_{CO} value
- Percentage predicted DL_{CO} value

Symptoms to consider severity

- Dyspnoea
- Dyspnoea/6-min walk test
- Blood oxygen saturation to desaturation
- Quality of life

5. Drivers of decision to initiate treatment (risk factors; screening results; diagnosis present at initiation)

- All patients who are severe should be offered pharmacological therapy
- Some patients with systemic sclerosis-associated ILD might not need pharmacological treatment
- In patients with systemic sclerosis-associated ILD who are not receiving pharmacological treatment, close follow up is required
- Clinical guidelines drive treatment recommendations in managing patients who are severe with systemic sclerosis-associated ILD
- When assessing the treatment, the following variables are valued:
  - Patient's quality of life
  - Scientific evidence of efficacy
  - Survival rate
  - Prolongation of time to progression
  - Safety and tolerability
  - Speed of improvement of patient's symptoms
  - Previous clinical experience

6. Which treatments are currently considered effective and are used in practice (at initiation)

- Mycophenolate mofetil
- Cyclophosphamide
- Monotherapy with corticosteroids is not an option

7. Options for follow-up assessments, and characteristics that indicate disease progression

Diagnosis tools for progression

- FVC
  - Percentage predicted FVC value
  - FVC at treatment initiation
  - Sustained FVC decline
  - Blood oxygen saturation to desaturation
- DL_{CO} (in combination with FVC)
  - Percentage predicted DL_{CO} value
  - DL_{CO} at treatment initiation
- HRCT
  - HRCT, change in extent or pattern can be used to assess severity of ILD
  - The decision to do HRCT is based on a combination of the current disease state and the speed of progression
  - Extent of fibrosis
- Worsening of symptoms

8. Drivers of decision to escalate treatment

- Patients whose disease is progressing or with inadequate response to treatment should be considered for treatment escalation

9. Which treatments are currently considered effective and are used in practice (at progression)

- Mycophenolate mofetil
- Cyclophosphamide
- Rituximab is a potential option
- Autologous haemopoietic stem-cell transplantation (agreed with appropriate caveats)
- Lung transplantation should be evaluated early especially in more advanced disease

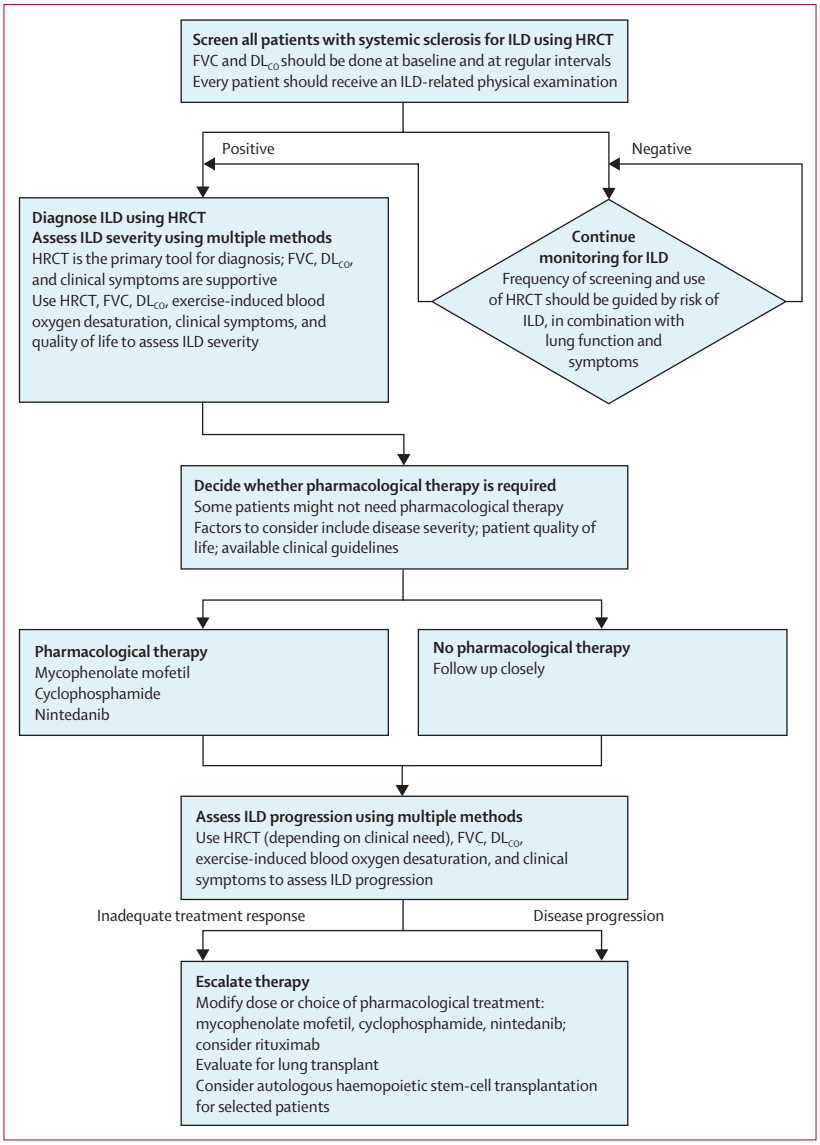

Figure 2: **Clinical management algorithm for systemic sclerosis-associated ILD**
This algorithm provides a brief summary of evidence-based consensus statements (including the supplemental Delphi process) for the identification and management of systemic sclerosis-associated ILD, for use in clinical practice. ILD=interstitial lung disease. HRCT=high-resolution CT. FVC=forced vital capacity. DL_{CO}=diffusing capacity of the lungs for carbon monoxide.

individual patient with systemic sclerosis-associated ILD, including clinical guidelines; clinical experience; patient survival rate; prolongation of time to progression; symptom improvement; quality of life; and efficacy, safety, and tolerability. No pharmacological treatment is an option for some patients with the condition, although all individuals with severe ILD should be offered treatment. Patients with early, stable, or mild disease should be followed up regularly and treatment initiated in cases of progression.[3] Mycophenolate mofetil and cyclophosphamide were agreed to be effective treatments for systemic sclerosis-associated ILD.[52–56] There was consensus disagreement that monotherapy with glucocorticoids is an effective treatment for the condition.[57] Consensus was not reached regarding use of tocilizumab,[58] azathioprine, or combination therapy (glucocorticoids plus other immunosuppressants).[57]

For disease progression, there was consensus agreement on several ways of assessing disease progression (in treated or untreated patients): changes in pulmonary function tests (FVC and DL_{CO} absolute values or FVC decline); changes in extent of fibrosis or pattern on HRCT; changes in exercise-induced oxygen desaturation; and worsening of clinical symptoms.[37,38,59–64] There was consensus disagreement on the usefulness of oesophageal diameter for indicating disease progression in patients with systemic sclerosis-associated ILD.[48] Additionally, one of the statements presented to the panel that generated the most discussion was that associated with the frequency and rationale for use of HRCT in patients with systemic sclerosis-associated ILD (table 2), which also reached consensus disagreement. Some panellists suggested that the frequency of HRCT measurements should depend on disease severity and progression, and it would not be possible to standardise a cadence for all patient subgroups. For the second round of voting, this statement was split into further statements to cover patients with different levels of severity and speed of progression. Subsequently, there was consensus agreement that the decision to use HRCT should be based on a combination of the current disease state and the speed of progression (table 1). For the algorithm (figure 2), HRCT use was therefore included as depending on clinical need. The threshold for consensus was not reached on whether all patients with mild (disagreement level 78%) or moderate (disagreement level 74%) systemic sclerosis-associated ILD should undergo HRCT assessment annually.[32]

For treatment escalation, pace of progression alongside disease severity helps drive decisions to escalate treatment in the experts' opinion. All patients with severe or progressive systemic sclerosis-associated ILD should be offered pharmacological treatment. If mycophenolate mofetil and cyclophosphamide are not appropriate, there was consensus that rituximab could be an option.[65–71] Autologous haemopoietic stem-cell transplantation and lung transplantation are effective treatments in subsets of patients with systemic sclerosis-associated ILD.[4,72–75] Lung transplant suitability should be evaluated early, particularly in patients diagnosed with advanced disease.[74,75] There were no consensus disagreement statements regarding treatment escalation.

14 statements relating to treatment initiation and escalation were tested across two supplemental Delphi rounds. Consensus agreement was reached on six statements (table 3); none of the remaining statements, including those relating to tocilizumab, reached the threshold for consensus. In summary, the panel agreed that nintedanib (as monotherapy or in combination with mycophenolate mofetil) might be an effective option for treatment initiation or escalation, subject to licensed availability. Mycophenolate mofetil or cyclophosphamide, or both,

	Score	Level of agreement
S4: Treatment initiation and options		
S4.1: Nintedanib is an effective treatment for patients with systemic sclerosis-associated ILD	6·1 (0·7)	100%
S4.2: Combination therapy (nintedanib and mycophenolate mofetil) is an effective treatment for patients with systemic sclerosis-associated ILD	6·3 (0·9)	95%
S6: Treatment escalation		
S6.1: Nintedanib is a treatment option for patients with systemic sclerosis-associated ILD, if mycophenolate mofetil or cyclophosphamide are not appropriate for patients	6·2 (0·7)	100%
S6.2: Mycophenolate mofetil or cyclophosphamide (or both) are treatment options for patients with systemic sclerosis-associated ILD, if nintedanib is not appropriate for patients	5·6 (1·4)	86%
S6.3: Combination therapy (nintedanib and mycophenolate mofetil) is a treatment option for patients with systemic sclerosis-associated ILD, if mycophenolate mofetil or cyclophosphamide as a single therapy are not appropriate for patients	6·1 (1·1)	91%
S6.4: Combination therapy (nintedanib and mycophenolate mofetil) is a treatment option for patients with systemic sclerosis-associated ILD, if nintedanib as a single therapy is not appropriate for patients	5·9 (1·5)	86%

Data are mean (SD) or %. Statements were rated from 1 (strong disagreement) to 7 (strong agreement). ILD=interstitial lung disease.

Table 3: **Expert consensus agreement statements on systemic sclerosis-associated ILD treatment (supplemental Delphi process)**

were considered options by the experts in cases in which nintedanib is not an appropriate choice for patients.

To make the consensus statements applicable for use in clinical practice, they were interpreted and incorporated into a management algorithm based on the expert opinion of the steering committee. This summary management algorithm for clinical practice is shown in figure 2. The clinical algorithm highlights that all patients with systemic sclerosis should undergo screening for ILD using HRCT. Close follow-up is suggested for patients with systemic sclerosis-associated ILD who do not require pharmacological treatment. Patients with evidence of disease progression or those with an inadequate response to treatment should be considered for treatment escalation, either by increasing the dose or by selecting an alternative therapy.

Discussion

The absence of consensus guidelines for screening, diagnosis, and management of systemic sclerosis-associated ILD makes early intervention difficult.[9] With use of a well established consensus method, a modified Delphi process, we have developed evidence-based expert consensus statements and defined an algorithm to provide clinical guidance for the identification and management of the condition.

These comprehensive consensus statements are the first to include six important management domains: (1) risk factors; (2) screening; (3) diagnosis and severity assessment; (4) treatment initiation and options; (5) disease progression; and (6) treatment escalation. Consensus agreement was reached that all patients with systemic sclerosis should be screened for lung fibrosis to enable early identification of ILD. The primary tool for screening and diagnosis of systemic sclerosis-associated ILD is HRCT, with pulmonary function outcomes and clinical symptoms providing supporting evidence. When ILD is present, the decision to treat should be based on disease severity and progression: patients with systemic sclerosis and severe or progressive ILD should be considered for treatment with mycophenolate mofetil, cyclophosphamide, or nintedanib, or with nintedanib in combination with mycophenolate mofetil, if appropriate. No consensus was reached regarding treatment with tocilizumab. These statements, based on robust methods and refined with use of expert clinician input, provide much needed clinical guidance in this complex patient group. Notably, the statements are up to date because a supplemental Delphi process was done including new therapy options for which clinical trials were recently published. By consolidating these statements into an algorithm, we believe they might be easily applicable in clinical practice.

The level of consensus reached for each statement reflects a balance between the quality of published evidence and expert opinion of usefulness in clinical practice. For example, statements on risk factors had high levels of supporting evidence but received many comments and had relatively low levels of consensus. Areas of low consensus in Delphi studies can highlight evidence gaps. In this case, it is apparent that more evidence is needed on the clinical utility of specific biomarkers (eg, Krebs von den Lungen-6 and surfactant protein D) as risk factors for ILD, the role of lung ultrasound in ILD screening and diagnosis, and screening frequency. More evidence is also required on the use of potential biomarkers, such as c-reactive protein,[76] for the prediction of disease progression and survival. Additionally, the role of oesophageal dilation or reflux disease in disease progression is not clear and more evidence is required; however, it might be prudent to counsel patients on the importance of reflux prevention until there is a definitive answer.

When robust clinical trial evidence is scarce, consensus cannot be achieved with certainty. This does not mean that further study evidence could not lead to robust consensus statements in the future. Lung ultrasound has shown its potential usefulness in studies, but has not yet reached the

level of evidence to be recommended as a reliable and sensitive diagnostic tool for systemic sclerosis-associated ILD.[49–51] More research is needed on optimal screening frequency in patients with systemic sclerosis at different levels of ILD risk, and on ways of reducing amounts of radiation exposure.[40] Reflecting this clinical uncertainty and the heterogeneity of systemic sclerosis-associated ILD, no definitive HRCT screening interval could be specified based on the current level of evidence. In terms of tools to assess severity of the condition, clinicians considered the measurement of dyspnoea as a respiratory symptom. Dyspnoea is established as a patient-centred outcome to assess the degree of difficulty in doing daily activities due to shortness of breath, and findings correlate with HRCT results.[45] Consensus on the optimal patient-reported outcome for measurement of dyspnoea in patients with systemic sclerosis-associated ILD would have been clinically useful, but was not raised in the discussions with the panel. Changes in pulmonary function over time might be sufficient to monitor disease progression, and the repeated use of HRCT could be guided by clinical decision.[25,32,37,38]

As more research is done and additional evidence becomes available, these statements might be updated accordingly, particularly with respect to the frequency of screening using HRCT and follow-up with pulmonary function tests, as these are areas that generated much discussion among the panellists, yet consensus was not reached.

The decision to initiate or escalate pharmacological therapy in patients with systemic sclerosis-associated ILD should be based on several factors in conjunction with clinical guidelines, clinician experience, and current evidence of efficacy, safety, and tolerability of available therapies. It is important to highlight that shared medical decision making with the patient is essential to balance risk and expected treatment outcomes with patient preference. The aim should be to improve patient symptoms and quality of life, delay disease progression, and prolong survival.[3] Clinical trial evidence indicates that mycophenolate mofetil is as effective as cyclophosphamide but better tolerated.[52–55] For treatments to be truly effective, symptomatic benefits should translate into reduced mortality, however improved survival has not yet been shown for these therapies.[56] Disease-modifying treatments for systemic sclerosis-associated ILD are currently under investigation.[7,77] For example, results from the SENSCIS study—published a few months after completion of the primary Delphi process—show that nintedanib significantly reduced the annual rate of decline in FVC compared with placebo in patients with systemic sclerosis-associated ILD, and supported treatment with nintedanib, either as monotherapy or in combination with mycophenolate mofetil.[19] Nintedanib has since been announced as the first US FDA-approved treatment to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated ILD,[10] although given that the disease has a long natural course and SENSCIS was a 52-week study, it has not yet been shown to prolong survival.

Our approach has several strengths. First, the robust consensus methods, including the number of panellists with their level of clinical expertise and experience across nine countries and from three specialties involved in the treatment of systemic sclerosis-associated ILD, adds validity to the consensus management algorithm developed during the modified Delphi process. Encouragingly, clinical practice was aligned across specialties. The retention rate in this study was 87%, indicating a high level of commitment by the panellists after more than 5 months of engagement and three primary Delphi rounds. The use of a strict consensus threshold (80%) ensured that only statements with strong support were included. Initial statements were based on a comprehensive systematic literature review and were refined by suggestions made by the panellists during the modified Delphi process. This method resulted in evidence-based statements that were considered straightforward and specific. The inclusion of a face-to-face discussion enabled the removal of possible ambiguity from the consensus statements and helped to ensure that the management algorithm was clinically relevant.[78]

This study had some limitations; for example, as with any Delphi process, it is difficult to qualify any possible external influences on opinions of the individual experts. In addition, as all panellists recruited to this study were based in Europe, there was no input from non-European experts, which can be considered a limitation. However, this is a field in which clinical practices can vary across different parts of the world and having a focus on one geographical area (ie, Europe) enabled alignment on practice for this region. Including experts from three specialities helped ensure a diverse range of participants. The fact that potential panel members were identified through review of recent guidelines (current and 2016), publications, and conferences related to systemic sclerosis-associated ILD (2018), rather than a random sample of clinicians that might treat patients with the disease, could suggest a potential for bias; however, it was decided that evidence of a certain level of experience in the management of patients with systemic sclerosis-associated ILD was necessary for optimal input into these consensus statements. No work was done to define mild, moderate, or severe disease, and a decision was taken to accept any bias that might have come from an absence of alignment among panellists on patient profile definitions. Furthermore, the Delphi method requires a high standard of published evidence; it was not the intention of this study to recommend novel or potential management approaches or treatments, which do not yet have a sufficient evidence base to support routine use in clinical practice. It is noteworthy that patients were not included in the present study. The inclusion of patients was not considered at study conception as our aim was to gain the first expert consensus for the identification and management of

systemic sclerosis-associated ILD. We therefore sought to recruit participants with a high level of clinical expertise who were able to evaluate the published evidence and provide optimal input into the consensus statements across all six domains, including risk factors, diagnosis, and assessment of severity. However, we acknowledge that patients and caregivers are increasingly recognised as key stakeholders in the development of guidance for clinical practice, and it would be pertinent to include patients or their representatives in further development of consensus recommendations. In addition, shared decision making between patients and clinicians was not discussed as part of the care of patients with systemic sclerosis-associated ILD, as there are no high-quality studies published to date, to our knowledge. However, this is an important point on the research agenda for the condition.

In conclusion, these evidence-based expert panel consensus statements, developed with a comprehensive modified Delphi process involving 27 rheumatologists, pulmonologists, and internists, provide guidance for the early identification and management of systemic sclerosis-associated ILD. By addressing emerging treatment options and when to initiate or escalate treatment in the disease, this effort will provide much-needed clinical guidance for the management of patients with systemic sclerosis at risk of ILD. We believe that the consensus statements and clinical practice algorithm will provide a framework for future treatment decision making.

Contributors

OD proposed the concept for the study and initiated discussions with Boehringer Ingelheim. The company had no role in the design of the study. A-MH-V, TMM, EEP, AA, and OD provided input into the conception and design of the study, were involved in interpretation of the study data, reviewed and revised the manuscript critically for important intellectual content, and approved the final version of the manuscript. The supplemental Delphi process was conceived and implemented by OD and A-MH-V. RB, SB, CB, PC, PEC, IC, FDG, JHWD, IF, PF, PMG, BG, AG-D-C, AMH, RH, MH, MK, FM-F, JO, SP, CR, MR-R, AS, MT, YU, UAW, and EW-S contributed to data generation, reviewed and revised the manuscript critically for important intellectual content, and approved the final version of the manuscript. The authors take full responsibility for the scope, direction, content of, and editorial decisions relating to the manuscript, were involved at all stages of development, and have approved the submitted manuscript. Treatment statements in the manuscript are reflective of the authors' opinions.

Declaration of interests

The authors received no direct compensation related to the development of the manuscript. All panellists were offered honoraria for their participation in the study. A-MH-V received an honorarium for participation in this study and received research funding and/or consulting fees or other remuneration from Actelion, Boehringer Ingelheim, and Roche. TMM received research funding and/or consulting fees or other remuneration from GlaxoSmithKline (GSK), UCB, Boehringer Ingelheim, AstraZeneca, Roche, Bayer, Biogen, Cipla, Prometic, and Sanumed; and has stock options or bond holdings in the for-profit corporation Apellis. EEP was an employee of IQVIA during the primary Delphi process. AA is an employee of IQVIA. CB received consulting fees from Actelion and Eli Lilly. PEC received research funding and/or consulting fees or other remuneration from Actelion, Roche, and Merck, Sharp & Dohme (MSD), and consultancy fees from Boehringer Ingelheim, GSK, VivaCell, and Emerald Health Pharmaceuticals. IC received consultancy fees and speaker honoraria from Actelion, Kern, BMS, Boehringer Ingelheim, Novartis, Pfizer, Gebro, and Nordic. FDG has received research funding and/or consulting fees or other remuneration from GSK, AstraZeneca, Boehringer Ingelheim, Actelion, Capella Bioscience, ChemomAb and Kymab. JHWD has consultancy relationships with Actelion, Active Biotech, AnaMar, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, JB Therapeutics, Medac, Pfizer, RuiYi, and Union Chimique Belge; received research funding from AnaMar, Active Biotech, Array Biopharma, aTyr, BMS, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, Novartis, Sanofi-Aventis, RedX, and UCB; and is stock owner of 4D Science. IF received an honorarium for participation in this study and received advisory fees from Bayer, Genentech, Sanofi, and Inventiva. PMG received research funding and/or consulting fees or other remuneration and non-financial support from Boehringer Ingelheim, consulting fees or other remuneration and non-financial support from Roche, and and consulting fees or other remuneration from Teva. BG received an honorarium for participation in this study. AGDC received consulting fees or other remuneration from Boehringer Ingelheim and Actelion. RH received consulting fees and/or speaker's honoraria from Boehringer Ingelheim, AbbVie, MSD, Novartis, Pfizer, UCB, Lilly, Roche, and Sanofi. MK received research funding and/or consulting fees or other remuneration from Boehringer Ingelheim and Roche, and consulting fees or other remuneration from AstraZeneca, GSK, and Galapagos. SP received an honorarium for participation in this study. CR received consulting fees or reimbursed travel from Actelion, AbbVie, Boehringer Ingelheim, BMS, GSK, Lilly, MSD, Novartis, and Pfizer. AS received an honorarium for participation in this study and received speaker fees from Actelion, BMS, and MSD. MT received an honorarium for participation in this study. YU received an honorarium for participation in this study; received consulting fees from Boehringer Ingelheim and Roche; and received non-financial support from Pfizer. UAW received consulting fees and research funding from Actelion, Bayer, Roche, Novartis, and Boehringer Ingelheim. EW-S received fees relating to participation in this study. OD received an honorarium for participation in this study, and has received research funding and consulting fees or other remuneration from Actelion, Bayer, Boehringer Ingelheim, and Mitsubishi, and has received consultancy or speaker fees from Abbvie, Acceleron Pharma, Amgen, AnaMar, Beacon Discovery, Blade Therapeutics, Catenion, CSL Behring, ChemomAb, Curzion Pharmaceuticals, Ergonex, Galapagos NV, Glenmark Pharma, GSK, Inventiva, Italfarmaco, iQone, Lilly, Medac, Medscape, Menarini, Mepha, MSD, Novartis, Pfizer, Roche, Sanofi, Target BioScience, and UCB in the area of potential treatments of scleroderma and its complications; in addition, OD has a patent microRNA-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143). All other authors declare no competing interests.

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