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Practice Guideline

ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR) Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG)

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Shareable abstract

This ERS/EULAR clinical practice guideline offers evidence-based recommendations on the screening, diagnosis, monitoring and treatment of CTD-ILDs. It emphasises the importance of further research in areas where evidence is lacking or certainty is low. https://bit.ly/4mX1bPB

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Background: Interstitial lung disease (ILD) is a frequent manifestation of connective tissue diseases (CTDs) and is associated with high morbidity and mortality. Clinical practice guidelines to standardise screening, diagnosis, treatment and follow-up for CTD-ILD are of high importance for optimised patient care.
Methods: A European Respiratory Society and European Alliance of Associations for Rheumatology task force committee, composed of pulmonologists, rheumatologists, pathologists, radiologists, methodologists and patient representatives, developed recommendations based on PICO (Patients, Intervention, Comparison, Outcomes) questions with grading of the evidence according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology and complementary narrative questions agreed on by both societies. For both PICO and narrative questions, the Evidence to Decision framework was used to formulate the recommendations.
Results: The task force committee concluded with recommendations for 25 PICO and 28 narrative questions, regarding ILD in the context of systemic sclerosis, rheumatoid arthritis (RA), idiopathic inflammatory myopathies, Sjögren disease (SjD), systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD). In four narrative questions, regarding screening and assessment of risk for ILD progression in MCTD, SjD and SLE and one PICO question regarding pirfenidone in CTD-ILD other than RA-ILD, the task force had insufficient evidence to support recommendations. Screening, diagnostic, monitoring and treatment algorithms were developed based on the recommendations and usual clinical practice.
Conclusions: We provide practical guidance by evidence-based recommendations to clinicians for each of the CTDs. In many cases there is low certainty or absence of evidence and we encourage further research to fill these gaps.

INTRODUCTION

Interstitial lung disease (ILD) is one of the most frequent manifestations in connective tissue diseases (CTDs) and is associated with high morbidity and mortality. International collaborations by pulmonology and rheumatology societies including patient research partners are important to develop guidelines with evidence-based approaches for screening, diagnosis, monitoring and treatment of ILD in CTDs for optimised management in clinical practice [1–3].

A collaborative effort between the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR) led to the formation of a task force aimed at developing clinical practice guidelines addressing these critical clinical aspects of CTD-ILD.

METHODS

Task force composition

The task force was approved by both societies (ERS and EULAR) and chaired by four experts (two from each society) and consisted of nine senior pulmonologists, nine rheumatologists, one radiologist and one histopathologist, and three early career members/fellows (supplementary file 1). Two patient representatives participated as full task force members in the guideline development and participated in all steps and meetings. Two more early career individuals contributed to the systematic reviews. Two ERS methodologists and one EULAR methodologist overviewed the guideline development process. The task force members were divided into four working groups covering screening, diagnosis/assessment of severity, monitoring and treatment, respectively. All potential conflicts of interest were disclosed by the task force members and managed according to society policies, and compliance was monitored by the chairs. The panel met numerous times in person and virtually. The guideline was developed following the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach as stated in the "memorandum of understanding" agreed on and signed by both ERS and EULAR.

Formulation of questions and selection of outcomes and their importance

Since CTD is a heterogeneous group of disorders, we assessed each question in four disease groups: systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), and other CTDs, including Sjögren disease (SjD), systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD). We included rheumatoid arthritis (RA) under the umbrella term CTD in this guideline. All task force members formulated PICO (Patients, Intervention, Comparison, Outcomes) (tables 1a and 1b) as well as narrative questions (tables 1a and 1c) [4], covering the key issues separately for each of the four pre-defined disease groups. For the PICO questions, the outcomes were rated as critical, important or not important for clinical decision-making, through anonymous online voting of all task force members, including the patient representatives [5]. Research priorities were formulated (table 1d). We only assessed critical or important outcomes.

Table 1a

Overview of recommendations grouped by screening, diagnosis, monitoring and treatment for patients with connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

Recommendations		Strength of recommendation	Level/certainty of evidence
Screening			
1) PICO 1–11	We recommend against replacing HRCT with pulmonary function tests for screening of ILD in patients with SSc, RA, IIM (S, L) and other CTDs (S, VL). We suggest not to replace HRCT with lung ultrasound for screening of ILD in patients with SSc, RA, IIM and other CTDs (C, L/VL).	S/C	L/VL
2) NQ 1–5	We recommend that all patients with SSc and MCTD and IIM patients with risk factors should be screened (S, L); and suggest that all patients with RA and SjD with risk factors, and IIM patients without risk factors (C, L) could be screened for ILD.	S/C	L
Diagnosis			
3) NQ 8–10	We suggest performing a global assessment of all risk factors of ILD progression in patients with SSc, RA and IIM to identify patients at higher risk of ILD progression and death.	C	L
4) NQ 12–13	We suggest that BAL could be used in patients with any CTD-ILD at the time of diagnosis in cases where there is suspicion of infection or to exclude alternative diagnoses. We suggest that lung biopsy should not play a role for diagnosis.	C	VL
5) NQ 14–19	We suggest using the 6MWT in patients without physical limitations and PROMs to assess severity and/or prognosis of ILD in any CTD-ILD patients.	C	L/VL
Monitoring			
6) NQ 20–27	We suggest repeating PFTs every 3–6 months during the first years, and at least every 6–12 months thereafter. We suggest regularly repeating HRCT after 1–2 years in patients with SSc-ILD, RA-ILD and other CTD-ILD, and after 3–6 months in IIM-ILD, particularly in those at higher risk of progression. We suggest repeating PFTs and HRCT in case of suspected progression in any CTD-ILD patient.	C	L/VL
Treatment			
7) PICO 12–15	We recommend using tocilizumab in a subgroup (S, M) and suggest using MMF, rituximab (C, VL), and cyclophosphamide (C, L) in patients with SSc-ILD.	S/C	M/L/VL
8) PICO 16	We recommend using immunosuppressive treatment in patients with IIM-ILD.	S	VL
9) PICO 17–18	We suggest using immunosuppressive treatment in patients with RA-, SjD-, MCTD- and SLE-ILD.	C	VL
10) PICO 19–20	We suggest using nintedanib in SSc-ILD (C, M) and in any CTD-ILD (C, VL) patient with progressive pulmonary fibrosis.	C	M/L/VL
11) PICO 21	We suggest using pirfenidone in patients with RA-ILD with a UIP pattern.	C	VL
12) PICO 23	We suggest using combination therapy with nintedanib and MMF in patients with SSc-ILD.	C	VL
13) PICO 24	We suggest using combination therapy with immunosuppressants including glucocorticoids in patients with IIM-ILD.	C	VL
14) PICO 25	We suggest treating patients with any CTD-ILD with a combination of immunosuppressants or, in the presence of progressive pulmonary fibrosis, with a combination of an immunosuppressant and nintedanib.	C	VL
15) NQ 28	We suggest using the inclusion criteria of RCTs to guide treatment decisions for CTD-ILD.	C	VL

PICO: Patients, Intervention, Comparison, Outcomes; NQ: narrative question; S: strong recommendation; C: conditional recommendation; M: moderate evidence; L: low evidence; VL: very low evidence; HRCT: high-resolution computed tomography; SSc: systemic sclerosis; IIM: idiopathic inflammatory myopathies; SjD: Sjögren disease; BAL: bronchoalveolar lavage; 6MWT: 6-min walk test; PROM: patient-reported outcome measure; PFT: pulmonary function test; MMF: mycophenolate mofetil; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; UIP: usual interstitial pneumonia; RCT: randomised controlled trial.

Table 1b

Task force recommendations for PICO (Patients, Intervention, Comparison, Outcomes) questions for connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

PICO question	Recommendations
Screening	
1) Should PFTs (FVC, D_{LCO}) be used as a replacement for HRCT to screen for ILD in patients diagnosed with SSc?	We recommend against replacing HRCT with PFTs for screening of ILD in patients with SSc (strong recommendation against, low certainty of evidence).
2) Should PFTs (FVC, D_{LCO}) be used as a replacement for HRCT to screen for ILD in patients diagnosed with RA?	We recommend against replacing HRCT with PFTs for screening of ILD in patients with RA (strong recommendation against, low certainty of evidence).
3) Should PFTs (FVC, D_{LCO}) be used as a replacement for HRCT to screen for ILD in patients diagnosed with IIM?	We recommend against replacing HRCT with PFTs for screening of ILD in patients with IIM (strong recommendation against, low certainty of evidence).
4) Should PFTs (FVC, D_{LCO}) be used as a replacement for HRCT to screen for ILD in patients diagnosed other CTDs?	We recommend against replacing HRCT with PFTs for screening of ILD in patients with other CTDs (strong recommendation against, very low certainty of evidence; no studies included).
5) Should LUS be used as a replacement for HRCT to screen for ILD in patients diagnosed with CTD?	We suggest not to replace HRCT with LUS for screening of ILD in patients with CTDs (conditional recommendation against, low certainty of evidence).
6) Should LUS with an extended protocol be used as a replacement for HRCT to screen for ILD in patients diagnosed with CTD?	We suggest not to replace HRCT with LUS with an extended protocol for screening of ILD in patients with CTDs (conditional recommendation against, very low certainty of evidence).
7) Should LUS with a short protocol be used as a replacement for HRCT to screen for ILD in patients diagnosed with CTD?	We suggest not to replace HRCT with LUS with a short protocol for screening of ILD in patients with CTDs (conditional recommendation against, low certainty of evidence).
8) Should LUS with an extended protocol be used as a replacement for HRCT to screen for ILD in patients diagnosed with SSc?	We suggest not to replace HRCT with LUS with an extended protocol for screening of ILD in patients with SSc (conditional recommendation against, very low certainty of evidence).
9) Should LUS with a short protocol be used as a replacement for HRCT to screen for ILD in patients diagnosed with SSc?	We suggest not to replace HRCT with LUS with a short protocol for screening of ILD in patients with SSc (conditional recommendation against, low certainty of evidence).
10) Should LUS be used as a replacement for HRCT to screen for ILD in patients diagnosed with RA?	We suggest not to replace HRCT with LUS for screening of ILD in patients with RA (conditional recommendation against, low certainty of evidence).
11) Should LUS be used as a replacement for HRCT to screen for ILD in patients diagnosed with other CTDs?	We suggest not to replace HRCT with LUS for screening of ILD in patients with other CTDs (conditional recommendation against, low certainty of evidence).
Treatment	
12) Should MMF *versus* control be used for patients with SSc-ILD?	We suggest using MMF in patients with SSc-ILD (conditional recommendation, very low certainty of evidence).
13) Should tocilizumab *versus* control be used for patients with SSc-ILD?	We recommend using tocilizumab in SSc-ILD patients with early diffuse cutaneous SSc and increased inflammatory markers or recent skin fibrosis progression (strong recommendation, moderate certainty of evidence).
14) Should rituximab *versus* control be used for patients with SSc-ILD?	We suggest using rituximab in patients with SSc-ILD (conditional recommendation, very low certainty of evidence).
15) Should cyclophosphamide *versus* control be used for patients with SSc-ILD?	We suggest using cyclophosphamide in patients with SSc-ILD (conditional recommendation, low certainty of evidence).
16) Should immunosuppressive treatment *versus* control be used for patients with IIM-ILD?	We recommend using immunosuppressive treatment in patients with IIM-ILD (strong recommendation, very low certainty of evidence).
17) Should immunosuppressive treatment *versus* control be used for patients with RA-ILD?	We suggest using immunosuppressive treatment in patients with RA-ILD (conditional recommendation, very low certainty of evidence).
18) Should immunosuppressive treatment *versus* control be used for patients with other CTD-ILD?	We suggest using immunosuppressive treatment in patients with SjD, MCTD and SLE-ILD (conditional recommendation, very low certainty of evidence; no studies included).
19) Should nintedanib *versus* control be used for patients with SSc-ILD?	We suggest using nintedanib in patients with SSc-ILD (conditional recommendation, moderate certainty of evidence).
20) Should nintedanib *versus* control be used for patients with any CTD-ILD?	We suggest using nintedanib in any CTD-ILD patients with progressive pulmonary fibrosis (conditional recommendation, low certainty of evidence).
21) Should pirfenidone *versus* control be used for patients with RA-ILD?	We suggest using pirfenidone in patients with RA-ILD with a UIP pattern (conditional recommendation, very low certainty of evidence).
22) Should pirfenidone *versus* control be used for patients with CTD-ILD other than RA-ILD?	No recommendation.
23) Should combination therapy with nintedanib and MMF *versus* control be used for patients with SSc-ILD?	We suggest using combination therapy with nintedanib and MMF in patients with SSc-ILD (conditional recommendation, low certainty of evidence).
24) Should combination therapy *versus* control be used for patients with IIM-ILD?	We suggest using combination therapy with immunosuppressants including glucocorticoids in patients with IIM-ILD (conditional recommendation, very low certainty of evidence).
25) Should combination therapy *versus* control be used for any patient with CTD-ILD?	We suggest treating patients with any CTD-ILD with a combination of immunosuppressants or, in the presence of progressive pulmonary fibrosis, with a combination of an immunosuppressant and nintedanib (conditional recommendation, very low certainty of evidence; no studies included).

PFT: pulmonary function test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; SSc: systemic sclerosis; IIM: idiopathic inflammatory myopathies; LUS: lung ultrasound; MMF: mycophenolate mofetil; SjD: Sjögren disease; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; UIP: usual interstitial pneumonia.

Literature review

Systematic literature searches were conducted for all questions. One information specialist designed and conducted the literature searches in multiple databases (PubMed, Cochrane Library and ClinicalTrials.gov), covering the years until 2022 (supplementary file 1). The reference lists of relevant systematic reviews and meta-analyses were also screened for relevant studies by the task force members, and some additional studies were included. Due to the excessive workload no update of the searches was conducted, but papers until December 2024 which the task force members deemed to be important were included. Screening of the identified studies was conducted by two task force members for each question; disagreements were resolved by a third member. Screening was conducted in two phases (title and abstract screening, and full-text screening). Inclusion and exclusion criteria, as well as the PRISMA flow diagrams [6], for each question are presented in supplementary file 1. For PICO

Table 1c

Task force recommendations for narrative questions for connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

Narrative question	Recommendations
Screening	
1) Which patients with SSc should be screened for ILD?	We recommend that all patients with SSc should be screened for ILD using HRCT (strong recommendation, low certainty of evidence stemming from narrative review).
2) Which patients with RA should be screened for ILD?	We suggest that patients with RA and risk factors for ILD including older age, smoking history, elevated rheumatoid factor, anti-CCP antibodies, increased inflammatory markers, male sex and high articular disease activity could be screened for ILD using HRCT (conditional recommendation, low certainty of evidence stemming from narrative review).
3) Which patients with IIM should be screened for ILD?	We recommend that patients with IIM and risk factors, including anti-synthetase syndrome, clinically amyopathic dermatomyositis, presence of mechanic's hands, arthritis and certain myositis-associated autoantibodies (anti-synthetase, anti-MDA-5 and anti-Ro52 antibodies), should be screened for ILD using HRCT (strong recommendation, low certainty of evidence stemming from narrative review).We suggest that most patients with IIM without risk factors could be screened for ILD using HRCT, except patients with inclusion body myositis (conditional recommendation, low certainty of evidence stemming from narrative review).
4) Which patients with MCTD should be screened for ILD?	We recommend that all patients with MCTD should be screened for ILD using HRCT (strong recommendation, low certainty of evidence stemming from narrative review).
5) Which patients with SjD should be screened for ILD?	We suggest that patients with SjD and risk factors including older age, male sex, active extrapulmonary organ involvement and increased inflammatory markers could be screened for ILD using HRCT (conditional recommendation, low certainty of evidence stemming from narrative review).
6) Which patients with SLE should be screened for ILD?	No recommendation.
7) How often should patients with CTD be screened for ILD?	No recommendation.
Diagnosisand monitoring	
8) How should patients with SSc be evaluated at baseline to assess risk of ILD progression or death?	We suggest performing a global assessment of all risk factors of ILD progression, including HRCT, PFTs (FVC and D_{LCO}), autoantibodies (particularly ATA-I), African American ethnicity, skin involvement (extent and progression) and markers of inflammation (CRP and/or ESR) to identify SSc-ILD patients at higher risk of ILD progression and death (conditional recommendation, low certainty of evidence stemming from narrative review).
9) How should patients with RA be evaluated at baseline to assess risk of ILD progression or death?	We suggest performing a global assessment of all risk factors of ILD progression, including UIP pattern and extent of ILD on HRCT, and PFTs (FVC and D_{LCO}) to identify patients with RA-ILD at higher risk of ILD progression and death (conditional recommendation, low certainty of evidence stemming from narrative review).
10) How should patients with IIM be evaluated at baseline to assess risk of ILD progression or death?	We suggest performing a global assessment of all risk factors of ILD progression, including HRCT, PFTs (FVC and D_{LCO}) and autoantibody profile (anti-MDA-5 antibody, anti-synthetase antibodies, anti-Ro52 antibody) to identify patients with IIM-ILD at high risk of ILD progression and death (conditional recommendation, low certainty of evidence stemming from narrative review).
11) How should patients with other CTDs be evaluated at baseline to assess risk of ILD progression or death?	No recommendation.
12) What is the role of BAL in patients with CTD-ILD at the time of diagnosis?	We suggest that BAL could have a role in patients with CTD-ILD at the time of diagnosis in cases where there is suspicion of infection or to exclude alternative diagnoses (conditional recommendation, very low certainty of evidence stemming from narrative review).
13) What is the role of lung biopsy in patients with CTD-ILD at the time of diagnosis?	We suggest that lung biopsy should not play a role at the time of diagnosis in patients with CTD-ILD (conditional recommendation against, very low certainty of evidence stemming from narrative review).
14) What is the role of the 6MWT in assessing severity and/or prognosis of ILD in patients with SSc?	We suggest using the 6MWT to assess severity and/or prognosis of ILD in SSc-ILD patients (conditional recommendation, low certainty of evidence stemming from narrative review).
15) What is the role of the 6MWT in assessing severity and/or prognosis of ILD in patients with RA?	We suggest using the 6MWT to assess severity and/or prognosis of ILD in RA-ILD patients with limited or no lower limb joint damage or active synovitis (conditional recommendation, very low certainty of evidence stemming from narrative review).
16) What is the role of the 6MWT in assessing severity and/or prognosis of ILD in patients with IIM?	We suggest using the 6MWT to assess severity of ILD in IIM-ILD patients without significant muscle involvement of the lower limbs (conditional recommendation, very low certainty of evidence stemming from narrative review).
17) What is the role of the 6MWT in assessing severity and/or prognosis of ILD in patients with other CTDs?	We suggest using the 6MWT to assess severity and/or prognosis of ILD in patients with other CTD-ILD (conditional recommendation, very low certainty of evidence stemming from narrative review).
18) What is the role of PROMs in assessing severity and/or prognosis of ILD in patients with SSc?	We suggest using PROMs to assess severity of ILD in patients with SSc-ILD (conditional recommendation, low certainty of evidence stemming from narrative review).
19) What is the role of PROMs in assessing severity and/or prognosis of ILD in patients with CTD other than SSc?	We suggest using PROMs to assess severity and/or prognosis of ILD in patients with CTD-ILD other than SSc-ILD (conditional recommendation, very low certainty of evidence stemming from narrative review).
Monitoring	
20) In patients with SSc-ILD being followed-up, when should PFTs be repeated?	We suggest repeating PFTs (FVC and D_{LCO}) every 3–6 months during the first 3–5 years for follow-up in patients with SSc-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, low certainty of evidence stemming from narrative review).
21) In patients with RA-ILD being followed-up, when should PFTs be repeated?	We suggest repeating PFTs (FVC, D_{LCO} and FEV_1 in view of the possible concomitant airway component) every 3–6 months during the first 1–2 years for follow-up in patients with RA-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).
22) In patients with IIM-ILD being followed-up, when should PFTs be repeated?	We suggest performing PFTs (FVC and D_{LCO}) every 3–6 months during the first year for follow-up in patients with IIM-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).

(*continued*)

Table 1c (***Continued***)

Narrative question	Recommendations
23) In patients with other CTD-ILD being followed-up, when should PFTs be repeated?	We suggest performing PFTs (FVC, D_{LCO} and FEV_1 in view of the possible concomitant airway component) every 3–6 months during the first year for follow-up in patients with SjD-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).No recommendation for SLE and MCTD.
24) In patients with SSc-ILD being followed-up, when should HRCT be repeated?	We suggest regularly repeating HRCT after 1–2 years in patients with SSc-ILD, particularly in those at higher risk of progression and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).
25) In patients with RA-ILD being followed-up, when should HRCT be repeated?	We suggest regularly repeating HRCT after 1–2 years in patients with RA-ILD, particularly in those at higher risk of progression and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).
26) In patients with IIM-ILD being followed-up, when should HRCT be repeated?	We suggest repeating HRCT after 3–6 months in patients at risk of developing severe or rapidly progressive IIM-ILD, annually over the first 2 years, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).
27) In patients with other CTD-ILD being followed-up, when should HRCT be repeated?	We suggest repeating HRCT after 1–2 years in patients with other CTD-ILD, particularly in those at higher risk of progression and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).
Treatment	
28) Can key factors be used for the choice of treatment for CTD-ILD?	We suggest using the inclusion criteria of RCTs to guide treatment decisions for CTD-ILD (conditional recommendation, very low certainty of evidence).

SSc: systemic sclerosis; HRCT: high-resolution computed tomography; IIM: idiopathic inflammatory myopathies; anti-CCP: anti-cyclic citrullinated peptide; anti-MDA-5: anti-melanoma differentiation-associated gene 5; MCTD: mixed connective tissue disease; SjD: Sjögren disease; SLE: systemic lupus erythematosus; PFT: pulmonary function test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; ATA-I: anti-topoisomerase I antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; UIP: usual interstitial pneumonia; BAL: bronchoalveolar lavage; 6MWT: 6-min walk test; PROM: patient-reported outcome measure; FEV_1: forced expiratory volume in the 1 s; RCT: randomised controlled trial.

Table 1d

Future research priorities and research agenda for connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

PICO/narrative question	Future research priorities
Should PFTs (FVC, D_{LCO}) be used as a replacement for HRCT to screen for ILD in patients diagnosed with CTD?	• Assess impact of screening with HRCT and PFTs over HRCT alone • Assess impact of screening of asymptomatic patients using clinical characteristics and/or biomarkers • Assess impact of early screening and diagnosis of ILD on outcomes
Should LUS be used as a replacement for HRCT to screen for ILD in patients diagnosed with CTD?	• Develop standardised screening protocols and validate them in prospective studies of asymptomatic patients, and organise educational and training programmes for LUS
Which patients with CTD should be screened for ILD?	• Identify novel risk factors, biomarkers or composite measures associated with ILD in CTDs • Explore genetic testing (*i.e.* MUC5B promoter risk variant) as a screening tool in RA patients • Assess impact of screening of RA, IIM and SjD patients with risk factors on outcome • Conduct multicentre, prospective investigations to determine the prevalence of ILD in all subtypes of other CTDs and risk factors predictive of the development of ILD
How often should patients with CTD be screened for ILD?	• Conduct multicentre, prospective investigations to determine the incidence of ILD in each CTD after initial negative screening and the risk factors predictive of development of ILD over time
How should patients be evaluated at baseline to assess risk of ILD progression or death?	• Conduct research studies, including large prospective multicentre design studies, to further assess how to define CTD-ILD progression • Develop a risk stratification tool to assess risk of CTD-ILD progression and to tailor differential upfront treatment strategies depending on risk of poor outcomes • Clarify the impact of RA activity on the prognosis of RA-ILD • In IIM: - Investigate and validate prognostic biomarkers in IIM-ILD across different ethnicities, as most published studies have been carried out in Asian cohorts - Further evaluate HRCT scores (including quantitative scores) to assess severity and predict risk of ILD progression in patients with anti-MDA-5 or anti-synthetase autoantibodies - Standardise myositis autoantibody assays
What is the role of BAL and/or lung biopsy in patients with CTD-ILD at the time of diagnosis?	• Assess novel biomarkers in BAL • Evaluate the use of cryobiopsy to better categorise fibrotic patterns • Evaluate the use of genomic subclassification *via* transbronchial lung biopsy • Assess the application of liquid biopsy in CTD-ILD in clinical practice
What is the role of the 6MWT in assessing severity and/or prognosis of ILD in patients with CTD?	• Conduct prospective studies to assess the role of the 6MWT in each CTD, including the prognostic role of: 1) desaturation thresholds and distance walked; 2) heart rate and dyspnoea recovery time, and blood pressure response; and 3) response to oxygen during the 6MWT in patients who experience oxygen desaturation • Explore the role of the "1-min sit to stand" test and whether it is a suitable alternative to the more cumbersome requirements of the 6MWT • Assess the role of remote 6MWT evaluation (*i.e.* at home, using mobile devices) • Especially for IIM, assess the prognostic impact of the 6MWT in the different stages of IIM-ILD, including in patients with rapidly evolving lung involvement.
What is the role of PROMs in assessing severity and/or prognosis of ILD in patients with CTD?	• Assess the association between PROMs and traditional severity measurements (*e.g.* HRCT, PFTs) • Evaluate the optimal frequency of PROM completion

(*continued*)

Table 1d (*Continued*)

PICO/narrative question	Future research priorities
In patients with CTD-ILD being followed-up, when should PFTs and HRCT be repeated?	• Conduct large prospective research studies with protocoled regular PFTs and chest HRCT at predefined intervals to establish an evidence-based algorithm for monitoring and risk stratification, and to decide on HRCT *versus* PFTs *versus* combination of both for long-term follow-up • Determine the ideal time intervals in each CTD depending on: 1) acute *versus* subacute *versus* chronic onset; 2) rapidly progressive *versus* chronic course of disease; and 3) different ILD subtypes; particularly in IIM this should be assessed depending also on different IIM subtypes and/or autoantibody status • Assess the role automated quantification of changes on HRCT • Assess the role of artificial intelligence for disease trajectory prediction • Assess the role of home-monitoring tools of lung function, oximetry and heart rate • Evaluate the ideal lung function parameters as outcome measures (FVC only, D_{LCO} only, combination/others) • In all, but particularly in SSc, assess the utility of repeating TLC measurements on follow-up
Should immunosuppressive treatment *versus* control be used for CTD-ILD?	• Identify and develop markers/tools for early detection and prediction of progression to enable timely treatment in patients at risk • Assess the molecular landscape to identify dysregulated pathways in SSc-ILD, including identification of disease-specific endotype targets • Assess long-term patient experiences and side-effects with acceptability (registry) studies in real-life cohorts • Assess 1) safety and efficacy of combination treatment (anti-fibrotic and immunosuppressive treatments); 2) novel treatment modalities, including CAR-T cells and bi-/tri-specific antibodies; and 3) MMF *versus* placebo in patients with very limited ILD in RCTs • Assess the efficacy of tocilizumab across the SSc-ILD population outside of early inflammatory SSc • Perform a large RCT of rituximab *versus* standard of care or other immunosuppressant • Conduct RCTs comparing the different treatment options in patients with RA-ILD • Evaluate in prospective collaborative studies the safety and efficacy of immunosuppressants in patients with SjD-, MCTD- and SLE-ILD; outcomes should include PFTs, HRCT, survival, symptoms and quality of life, with a long-term perspective • Specific topics for IIM-ILD include: - Conduct RCTs allowing background therapy - Identify the best treatment options for the different subgroups of IIM - Evaluate disease specific PROMs of immunosuppressants in IIM-ILD and novel treatment modalities, including CAR-T cells, bi-/tri-specific antibodies, and plasmapheresis - Conduct randomised clinical trials of IVIG *versus* placebo for the treatment of ILD
Should anti-fibrotic medication *versus* control be used for patients with CTD-ILD?	• On top of general priorities, assess effects of pirfenidone and nintedanib on mortality and long-term outcomes • Assess efficacy of pirfenidone in patients with different HRCT patterns (UIP *versus* NSIP)
Should combination therapy *versus* control be used for patients with CTD-ILD?	• Assess efficacy and safety studies of novel agents in combination, both upfront combination and sequential to prevent ILD progression and lung damage • Evaluate safety, efficacy, side-effects and acceptability of combination treatment with anti-fibrotics and immunosuppressants or combined immunosuppressants or immunosuppressants with glucocorticoids, including evaluation on the lung and other organ manifestations • Evaluate long-term patient experience data, effect on quality of life and symptom/side-effects burden
Non-pharmacological management	• The role of non-pharmacological management has not been addressed in this guideline but is of great importance • Evaluate lung transplant across CTD-ILD populations • Determine the role of oxygen use across CTD and RA-ILD populations • Assess the role of palliative measures
Can key factors be used for the choice of treatment for CTD-ILD?	• Identify and develop key factors for choice of treatment for ILD in CTD-ILD to enable timely treatment with the right intervention on an individual level, including analysis of registry data • Determine the safety and efficacy of specific interventions using key factors for choice of treatment for ILD in CTD-ILD in clinical trials

SSc: systemic sclerosis; PICO: Patients, Intervention, Comparison, Outcomes; PFT: pulmonary function test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; LUS: lung ultrasound; IIM: idiopathic inflammatory myopathies; SjD: Sjögren disease; anti-MDA-5: anti-melanoma differentiation-associated gene 5; BAL: bronchoalveolar lavage; 6MWT: 6-min walk test; PROM: patient-reported outcome measure; TLC: total lung capacity; CAR-T cell: chimeric antigen receptor T-cell; MMF: mycophenolate mofetil; RCT: randomised controlled trial; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; IVIG: intravenous immunoglobulin; UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia.

questions, whenever available, randomised controlled trials (RCTs) were the main body of evidence; if these were not available, observational studies were chosen. In absence of direct evidence (RCTs and observational studies), indirect evidence was used to formulate recommendations, if possible, as explained in supplementary file 1. If deemed appropriate by the task force members, evidence was extrapolated from one CTD to another to support formulating recommendations. For treatment PICO questions the task force agreed to not extrapolate from one disease to another.

Evidence syntheses and assessment of the certainty of evidence

PICO questions were assessed *via* full systematic review, including risk of bias assessment and grading of the evidence [7]. Narrative questions were assessed *via* systematic literature searches and narrative review of the evidence [4]. If appropriate, meta-analyses were conducted using RevMan 5.4 software [8]. The certainty of evidence was rated using the GRADE approach. For each PICO, GRADE evidence profiles were formulated using the GRADEpro tool (www.gradepro.org/) (supplementary file 2) [7]. The final certainty of evidence for each question was rated as high, moderate, low or very low.

Formulating recommendations

All PICO and narrative questions were phrased by all task force members. For both PICO and narrative questions, the Evidence to Decision (EtD) framework was used to transparently document the process of making recommendations (supplementary file 2). An overview of PICO and narrative questions, explanation, consideration and remarks is given in table 2 and for

TABLE 2

Overview of PICO (Patients, Intervention, Comparison, Outcomes) and narrative questions (NQs), explanation, considerations and remarks for screening, diagnosis and monitoring for connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

	Explanation	Considerations and remarks
PICO 1–4: Should PFTs (FVC and D_{LCO}) be used as a replacement for HRCT to screen for ILD in patients diagnosed with CTD?	We assessed whether PFTs could replace HRCT as a screening tool for ILD in patients with CTDs. The populations were patients diagnosed with the respective CTD (SSc, RA, IIM or other CTDs), the intervention PFTs (FVC or D_{LCO}), the comparator HRCT and the outcome was the identification of ILD.	Although PFTs should not replace HRCT for screening, PFTs and assessment of respiratory symptoms are deemed important for functional and symptomatic assessment.
PICO 5–11: Should LUS be used as a replacement for HRCT to screen for ILD in patients diagnosed with CTD?	We assessed whether LUS could replace HRCT as a screening tool for ILD. The protocols of LUS found in the literature were divided into extended protocol, where the sonographers quantified B-lines (lung comet tails) in more than 18 intercostal spaces bilaterally, and the short protocol, where the quantification was conducted in 18 or fewer intercostal spaces bilaterally. Seven PICOs were formulated, where the population were patients diagnosed with CTDs (generally CTDs, SSc, RA or other CTDs including SjD, IIM and SLE), the intervention LUS (extended and/or short protocol), the comparator HRCT and the outcome the identification of ILD.	LUS can be performed at the bedside, is low-cost, non-invasive, and without radiation for the patient. However, it requires well-trained operators, the examination and its results are highly user-dependent, and B-lines are not specific for ILD.
NQ 1–6: Which patients with CTD should be screened for ILD?	The NQ assessed whether risk factors exist that could enable selection of patient populations for screening of ILD. Predefined risk factors included extrapulmonary CTD features, demographic factors, genetics, constitutional symptoms, clinical examination, the presence of some clinical biomarkers (*e.g.* autoantibodies, inflammatory markers) and environmental factors (*e.g.* smoking). The outcome was presence of ILD on HRCT.	
NQ 7: How often should patients with CTD be screened for ILD?	The NQ addressed how often CTD patients should be screened after initial negative screening to detect incident ILD. Studies assessing the frequency of development of incident ILD on HRCT were included.	
NQ 8–11: How should patients with CTD-ILD be evaluated at baseline to assess risk of ILD progression or death?	These NQs addressed whether risk factors exist to assess risk of worse outcomes, including risk of progression and death. Only baseline factors currently in widespread clinical use were included. Novel and/or not widely available biomarkers were excluded.	Remarks and considerations for all sub-questions: The risk factors addressed below are associated with worse outcome at a population level, recognising that it is not possible in any individual patient to confidently exclude the risk of progression or death.
NQ 12–13: What is the role of BAL and/or lung biopsy in patients with CTD-ILD at time of diagnosis?	The following NQs address the utility of BAL and/or lung biopsy at the time of diagnosis for patients diagnosed with ILD on HRCT.	BAL and lung biopsy are invasive and thus may be uncomfortable for the patient, and may associate with complications, including acute ILD exacerbation, bleeding and pneumothorax, which in specific cases can lead to worsening of morbidity and mortality. Thus, a multidisciplinary team discussion for individual cases is suggested to decide if BAL or lung biopsy is required, to balance risks and benefits and to decide how the result of these examinations might alter management. In cases of differential diagnosis including suspected malignancy, lung biopsy might be needed, while especially in low-grade lymphomas BAL clonality and diagnostic flow cytometry might be adequate for the diagnosis without tissue.
NQ 14–17: What is the role of the 6MWT in assessing severity and/or prognosis of ILD in patients with CTDs?	This NQ addressed whether 6MWT, including oxygen desaturation on exertion, has a role in the assessment of severity and/or as a prognostic marker in patients diagnosed with CTD-ILD.	CTD-ILD patients often have extrapulmonary organ manifestations or treatment-related factors (*e.g.* glucocorticoids), which can influence the 6MWT, such as significant skin fibrosis, vascular and musculoskeletal impairment in SSc; lower limb joint deformity, active synovitis and/or structural damages resulting from synovitis in RA; significant musculoskeletal involvement (severe myalgia, muscle weakness, arthritis) in IIM; and specific CTD manifestations, such as severe myalgia, muscle weakness and arthritis in other CTDs. The coexistence of pulmonary hypertension may also influence the performance of the 6MWT and oxygen desaturation.
NQ 18–19: What is the role of PROMs in assessing severity and/or prognosis of ILD in patients with CTDs?	The NQ addressed whether PROMs to assess symptom and disease burden and patient needs have a role in the assessment of severity and/or as a prognostic marker in patients diagnosed with CTD-ILD. We included any identified PROM.	Clinicians should not rely only on results of PROMs to assess severity and/or prognosis of ILD in patients with CTD, as associations between PROMs and traditional severity and/or prognostic measurements (such as HRCT and PFTs) are weak. However, PROMs may complement other severity and/or prognosis assessments as they reflect a different and patient-centred domain. Due to the various PROMs assessed, no specific PROMs can be recommended or suggested.
NQ 20–23: In patients with CTD-ILD being followed-up, when should PFTs be repeated?	These NQs address the timeframe in which PFTs should be repeated for the monitoring of patients diagnosed with CTD-ILD.	FVC is considered the most accurate measurement for follow-up of ILD, although fall in D_{LCO} may also reflect progression of ILD. An isolated worsening in D_{LCO} may signify concomitant development of pulmonary hypertension. Therefore, both measurements should be monitored in follow-up.
NQ 24–27: In patients with CTD-ILD being followed-up, when should HRCT be repeated?	These NQs addressed the timing in which HRCT should be repeated for monitoring of patients diagnosed with CTD-ILD, as well as the time intervals between repeat follow-up HRCT.	HRCT may also be useful to rule out other causes of worsening of patients, *e.g.* infections or cancer. Repeating HRCT instead of PFTs may be considered in critically ill patients not able to perform PFTs. For repeat HRCT as regular follow-up, low dose radiation protocols may be considered.

PFT: pulmonary function test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; SSc: systemic sclerosis; IIM: idiopathic inflammatory myopathies; LUS: lung ultrasound; SjD: Sjögren disease; SLE: systemic lupus erythematosus; BAL: bronchoalveolar lavage; 6MWT: 6-min walk test; PROM: patient-reported outcome measure.

treatment in the treatment section. Recommendations were graded as strong or conditional [9–11]. The EtD tables and recommendations, strength and direction of the recommendation were discussed in panel meetings, and consensus was reached. The recommendations were phrased using "recommend" and "should" for strong recommendations and "suggest" and "could" for conditional recommendations. We prepared algorithms covering screening, diagnosis, monitoring and treatment based on the PICO and narrative questions, and added usual clinical practice. The chairs drafted the manuscript, which was then reviewed and approved by all co-authors.

SCREENING FOR ILD IN CTDS

General considerations

ILD is a frequent manifestation and associates with high morbidity and mortality across CTDs. In this guideline, we included RA under the umbrella term CTD. Screening is important for early diagnosis of ILD, enabling early interventions. Optimal screening tools and guidance on how often patients should be screened are important.

PICO questions 1–4

Should pulmonary function tests (PFTs) (forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (D_{LCO})) be used as a replacement for high-resolution computed tomography (HRCT) to screen for ILD in patients diagnosed with SSc, RA, IIM or other CTD-ILD?

Recommendation

We recommend against replacing HRCT with pulmonary function tests for screening of ILD in patients with SSc, RA, IIM and other CTDs (strong recommendation against, low certainty of evidence for SSc, RA and IIM, and very low certainty of evidence (no studies included) for other CTDs).

Summary of evidence

For SSc: In nine observational studies [12–20], including 1696 SSc patients with ILD and 1495 without ILD, the sensitivity varied between 34% and 92%, and the specificity between 38% and 96%. In several studies, PFTs were inaccurate, missing between 6% and 88% of patients with ILD. The number of correctly identified cases (true-positives) ranged from 190 to 480 per 1000 patients tested, assuming a pre-test probability of 50%. Missed cases of ILD (false-negatives) varied between 20 and 310 per 1000 patients. The number of correctly identified cases (true-negatives) ranged from 170 to 460 per 1000, while false-positive cases ranged from 40 to 330 per 1000 patients. There was risk of bias and inconsistency, leading to an overall low certainty of evidence.

For RA: In four selected articles based on observational cohorts [21–24], including 96 patients with ILD and 191 without ILD, the sensitivity varied between 58% and 99%, and the specificity between 48% and 96%. The number of correctly identified cases (true-positives) ranged from 41 to 69 per 1000 at pre-test probabilities of 7%, and from 191 to 327 per 1000 at pre-test probabilities of 33%. Missed ILD (false-negatives) ranged from 1 to 29 per 1000 at 7% pre-test probability, and 3 to 139 per 1000 at 33% pre-test probability. The number of correctly identified cases (true-negatives) ranged from 446 to 893 per 1000 at 7% pre-test probability, and from 322 to 643 per 1000 at 33% pre-test probability. Additionally, there were false-positive cases ranging from 37 to 484 per 1000 at 7% pre-test probability, and 27 to 348 per 1000 at 33% pre-test probability. There was risk of bias and inconsistency, therefore the overall certainty of evidence was low.

For IIM: Across two observational studies [25,26], including 23 patients with and 74 without ILD, the sensitivity ranged from 69% to 100% and the specificity ranged from 67% to 99%. The number of correctly identified cases (true-positives) ranged from 138 to 200 per 1000 at pre-test probabilities of 20%, and from 593 to 860 per 1000 at pre-test probabilities of 86%. Missed ILD (false-negatives) ranged from 0 to 62 per 1000 at 20% pre-test probability, and 0 to 267 per 1000 at 86% pre-test probability. The number of correctly identified cases (true-negatives) ranged from 536 to 792 per 1000 at 20% pre-test probability, and from 94 to 139 per 1000 at 86% pre-test probability. False-positive cases ranged from 8 to 264 per 1000 at 20% pre-test probability, and 1 to 46 per 1000 at 86% pre-test probability. There was indirectness and imprecision, therefore the overall certainty of evidence was low.

For other CTDs: There were no studies identified that addressed the role of PFTs for ILD screening in patients diagnosed with other CTDs. We used indirect evidence and extrapolation from SSc-ILD, RA-ILD and IIM-ILD to reach a recommendation. Indirect evidence included two observational studies [27,28], including patients with different CTD diagnoses including other CTD-ILD patients were identified and showed varying sensitivity ranging from 55% to 96%, and specificity from 36% to 78.5%, across all CTD-ILD patients. No subgroup analyses on any other CTD-ILD were conducted.

Justification of recommendation

We recommend that PFTs should not replace HRCT for the screening of ILD in patients with SSc, RA, IIM and other CTDs, as PFTs were not able to identify those with and without ILD with sufficient accuracy. The certainty of evidence was low for SSc, RA and IIM and very low for other CTDs stemming from indirect and extrapolated data, but the strong recommendation is based on the high likelihood of missing ILD if PFTs are used as the only screening tool. Missing the diagnosis of ILD in patients with CTD is associated with a lost opportunity of intervention, and increased mortality and morbidity. Given the high prevalence of ILD in SSc and IIM, and that undiagnosed ILD is associated with significantly higher morbidity and mortality, the risk of missing the diagnosis is too great to justify screening by PFTs only. Missing the diagnosis of ILD in any patients with RA and other CTDs is associated with a lost opportunity of intervention, and increased mortality and morbidity. The undesirable effects, such as radiation exposure from using HRCT, are considered lower than the desirable effects of early and accurate ILD detection.

PICO questions 5–11

Should lung ultrasound (LUS) be used as a replacement for HRCT to screen for ILD in patients diagnosed with SSc, RA, IIM or other CTDs?

Recommendation

We suggest not to replace HRCT with LUS for screening of ILD in patients with SSc, RA, IIM and other CTDs (conditional recommendation against, low certainty of evidence for any LUS in SSc, RA, IIM and other CTDs, low certainty of evidence for short protocol in all and SSc, and for extended protocol for all and SSc very low certainty of evidence).

Summary of evidence

The included studies used different ultrasound scanning protocols and different definitions of a positive LUS scan. We therefore show the results of all studies and divide by shorter and extended protocols using 18 B-lines as the cut-off. In 12 observational cohort studies (n = 971) [18,29–39], the sensitivity of LUS to detect ILD was 94% (95% CI 0.87 to 0.97) and the specificity 86% (95% CI 0.75 to 0.93). A substantial number of the included patients were without respiratory symptoms, but detailed information was not given in all studies. A percentage of ILD diagnoses would be missed as false-negatives (49 of 971 patients) or would be misdiagnosed with ILD as false-positives (71 of 971 patients) when screened only with LUS. The overall certainty of evidence was rated low because of serious risk of bias and indirectness. Five of the 12 cohort studies comparing LUS with HRCT for the screening of ILD in patients with CTD used an extended protocol. In these (n = 545) [18,29,30,33,35], the sensitivity of LUS to detect ILD was 97% (95% CI 0.87 to 0.99) and the specificity 82% (95% CI 0.43 to 0.96). There were false-negatives (17 of 545 patients) and false-positives (51 of 545 patients). The overall certainty of evidence was rated very low because of serious risk of bias, indirectness and imprecision. Eight of the 12 cohort studies identified comparing LUS with HRCT for the screening of ILD in patients with CTD used a short protocol. In these (n = 495) [31–34,36–39], the sensitivity of LUS to detect ILD was 90% (95% CI 0.80 to 0.95) and the specificity 88% (95% CI 0.83 to 0.92). There were false-negatives (28 of 495 patients) and false-positives (37 of 495 patients). The overall certainty of evidence was rated low because of serious risk of bias and indirectness. Four of the eight cohort studies comparing LUS with HRCT for the screening of ILD in patients with SSc used an extended protocol. In these (n = 369) [18,29,33,35], the sensitivity of LUS to detect ILD was 98% (95% CI 0.88 to 1.00) and the specificity 64% (95% CI 0.38 to 0.84). There were false-negatives (16 of 369 patients) and false-positives (50 of 369 patients). The overall certainty of evidence was rated very low, because of serious risk of bias, indirectness and imprecision. Five of the eight cohort studies comparing LUS with HRCT for the screening of ILD in patients with SSc used a short LUS protocol. In these (n = 295) [31,33,37–39], the sensitivity of LUS to detect ILD was 91% (95% CI 0.78 to 0.97) and the specificity 85% (95% CI 0.77 to 0.91). There were false-negatives (17 of 295 patients) and false-positives (24 of 295 patients). The overall certainty of evidence was low because of serious risk of bias and indirectness. Two observational cohort studies compared LUS with HRCT for the screening of ILD in patients with RA. In these studies (n = 138) [34,36], both the sensitivity (95% CI 0.81 to 0.98) and specificity (95% CI 0.85 to 0.96) of LUS to detect ILD were 93%. There were false-negatives (3 of 138 patients) and false-positives (7 of 138 patients). In the included studies, a short LUS protocol was used and no comparison with an extended LUS protocol could be made. The overall certainty of evidence was rated low, because of serious risk of bias and indirectness. Two observational cohort studies compared LUS with HRCT for the screening of ILD in a pooled population of patients with other CTDs (including SjD, IIM and SLE). In these studies (n = 238 with various systemic autoimmune diseases including 47 with SjD, 19 with IIM, and 25 with SLE) [30,32], the sensitivity of LUS to detect ILD was 91% (95% CI 0.74 to 0.97) and the specificity 95% (95% CI 0.86 to 0.98). There were false-negatives (11 of 238 patients) and false-positives (5 of 238 patients). In one of the included studies a short LUS protocol was used, while in the other an extended LUS protocol was used, and no comparison between the two LUS protocols could be made. The overall certainty of evidence was rated low because of serious risk of bias and indirectness.

Justification of recommendation

We suggest not to replace HRCT with LUS for screening of ILD in patients with CTD due to the possibility of false-negative results where patients would face a delay in the start of the recommended treatment, false-positive results where patients may undergo unnecessary investigations and/or treatment, and the very low certainty of evidence. Current challenges are inherent to implementing LUS widely in clinical practice.

Narrative question 1

Which patients with SSc should be screened for ILD?

Recommendation

We recommend that all patients with SSc should be screened for ILD using HRCT (strong recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

The review of 26 observational studies [13,14,19,40–62] evaluating risk factors for ILD in SSc encompassed 8898 patients. Diffuse cutaneous SSc was a risk factor for ILD across 10 out of 12 studies [19,40,42,46,52,53,55–58,60,61]. Skin involvement, particularly the modified Rodnan skin score (mRSS) was higher in patients with ILD *versus* no ILD. Auto-antibodies, including anticentromere antibody (ACA), anti-topoisomerase I antibody (ATA-I) and anti-RNA polymerase III antibody, showed significant associations with ILD, with ATA-I consistently linked to ILD across eleven studies [19,40,41,47–49,51–53,56,62], and ACA negatively associated with ILD in nine studies [13,19,40,48,53,56,57,60,62].

Justification of recommendation

We recommend screening all patients with SSc for ILD using HRCT, as the risks of HRCT, such as radiation exposure, are minimal, and HRCT is the preferred method by patients. While the certainty of evidence is low, the strong recommendation is based on the high risk of missing ILD if screening by HRCT is limited to patients with certain risk factors, as the prevalence of ILD is high in SSc and none of the risk factors are definitively linked to the presence or absence of ILD. Limiting screening to a subset of patients would result in missing a meaningful number of cases with ILD, which would result in increased morbidity and mortality.

Narrative question 2

Which patients with RA should be screened for ILD?

Recommendation

We suggest that patients with RA and risk factors for ILD, including older age, smoking history, elevated rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, increased inflammatory markers, male sex and high articular disease activity, could be screened for ILD using HRCT (conditional recommendation, low certainty of evidence stemming from narrative review).

Remarks and considerations

Experience from clinical practice suggests that patients with multiple risk factors should be considered for ILD screening

using HRCT. It is of high importance to assess the presence of risk factors for ILD in every RA patient.

Summary of evidence

In total, 15 observational studies [63–77] evaluated risk factors for ILD in RA or assessed differences between subgroups with and without ILD (or healthy controls), including 4012 patients with RA and 45 healthy controls. Conflicting evidence existed for disease duration, with one study highlighting a longer disease duration among ILD patients [64], while another suggested a correlation between ILD development and a short RA disease duration (<5 years) [72]. Six studies reported a significant association between older age at the onset of RA and ILD in RA [64,66,70–72,75]. Two studies identified male sex as an independent risk factor for ILD in RA [70,72] and four studies demonstrated a significant association between smoking and ILD [63,65,74,75]. Four studies found associations between increased articular disease activity, including higher disease activity scores, swollen joint counts and serositis with RA-ILD [64,66,70,74]. RF and anti-CCP antibodies were identified as risk factors for ILD in six [66,67,69,72,76,77] and four [68,75–77] studies, respectively. Erythrocyte sedimentation rate (ESR) was reported to be higher in RA-ILD than in RA without ILD in three studies [67,70,71].

Justification of recommendation

We suggest that patients with RA at risk for ILD could be screened for ILD using HRCT. This recommendation is conditional due to the low certainty of evidence and the lower overall prevalence of ILD in RA. However, not screening at-risk RA patients with HRCT could lead to missing a significant number of ILD cases, which may increase morbidity and mortality. The risks associated with HRCT, such as radiation exposure, are minimal, and HRCT is generally preferred by patients.

Narrative question 3

Which patients with IIM should be screened for ILD?

Recommendation 1

We recommend that patients with IIM and risk factors, including anti-synthetase syndrome, clinically amyopathic dermatomyositis (CADM), presence of mechanic's hands, arthritis and certain myositis-associated autoantibodies (anti-synthetase, anti-melanoma differentiation-associated gene 5 (anti-MDA-5) and anti-Ro52 antibodies), should be screened for ILD using HRCT (strong recommendation, low certainty of evidence stemming from narrative review).

Recommendation 2

We suggest that most patients with IIM without risk factors could be screened for ILD using HRCT, except patients with inclusion body myositis (conditional recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

We identified 20 observational studies [25,78–96] and one systematic review with meta-analysis [97] assessing risk factors for ILD in patients with IIM. These included 4591 patients with IIM and 12 healthy controls; and 2079 patients (834 patients and 1245 controls) in the meta-analysis. CADM and anti-synthetase syndrome were associated with higher prevalence of ILD, but ILD also occurred in other dermatomyositis and polymyositis. Disease duration in IIM was infrequently associated with ILD. The meta-analysis revealed an increased ILD risk with older age at IIM diagnosis, while sex showed no discernible impact on ILD prevalence [97]. Skin involvement, arthritis/arthralgia and fever emerged as risk factors for ILD. Anti-RNA synthetase autoantibodies, particularly anti-Jo-1, as well as anti-MDA-5 autoantibodies, were consistently linked to ILD across studies and confirmed in the meta-analysis. Additionally, anti-Ro52 was associated with ILD [25,78–97]. Elevated ESR and C-reactive protein (CRP) were consistently associated with ILD across three studies [81,84,90] and in the meta-analysis [97].

Justification of recommendation

We recommend that patients with IIM at risk for ILD should be screened for ILD using HRCT. The certainty of evidence was low, but our recommendation to screen IIM patients at risk for ILD is strong because the risks of HRCT, such as radiation exposure, are minimal, and HRCT is the preferred method by patients. Not screening IIM patients at risk for ILD using HRCT would result in missing a meaningful number of cases with ILD, which could result in increased morbidity and mortality.

We suggest that, in the absence of identified risk factors, all patients with IIM, except those with inclusion body myositis, could be screened for ILD using HRCT. This recommendation is conditional based on the low certainty of evidence and the lower prevalence of ILD in IIM patients without risk factors and in patients with inclusion body myositis. However, the risks associated with HRCT, such as radiation exposure, are minimal, and none of the risk factors are definitively linked to the presence or absence of ILD. As a result, failing to screen could lead to missed ILD cases, increasing morbidity and mortality.

Of note, we looked at evidence for other CTDs and found 12 studies in total. Due to the different included patient populations we decided to separate them and report separately by underlying other CTDs (narrative questions 4–6).

Narrative question 4

Which patients with MCTD should be screened for ILD?

Recommendation

We recommend that all patients with MCTD should be screened for ILD using HRCT (strong recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

Two observational studies [98,99] on MCTD included 277 patients, of which 130 had ILD. In one study, CRP levels, antinuclear ribonucleoprotein (U1RNP) antibodies, dyspnoea and tachycardia were identified as risk factors for ILD [98], while the other focused on anti-Ro52 antibodies [99].

Justification of recommendation

We recommend screening all patients with MCTD for ILD using HRCT, as the risks, such as radiation exposure, are minimal, and HRCT is generally preferred by patients. Although the certainty of the evidence is low, this strong recommendation is driven by the high likelihood of missing ILD if screening is restricted to patients with specific risk factors. The prevalence of ILD in MCTD is high, and no risk factors are definitively linked to the presence or absence of ILD. Additionally, phenotypic similarities to SSc were considered. Limiting screening to only a subset of patients would likely result in missing a significant number of ILD cases, leading to increased morbidity and mortality.

Narrative question 5

Which patients with SjD should be screened for ILD?

Recommendation

We suggest that patients with SjD and risk factors including older age, male sex, active extrapulmonary organ involvement and increased inflammatory markers could be screened for ILD using HRCT (conditional recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

Seven observational studies including 2608 SjD patients of which 764 had ILD and one meta-analysis including 23 studies and 6157 SjD patients [100–107] assessed risk factors for ILD in SjD. Two studies identified anti-Ro52 autoantibodies [100,101], while one identified higher lactate dehydrogenase levels as risk factor for ILD [101]. Older age was consistently associated with ILD. Other factors, such as Raynaud's phenomenon, lymphopenia, rampant dental caries, oesophageal involvement, multi-organ disease, menopausal status, low albumin levels and smoking, were associated in individual studies [100–103,105–107]. The meta-analysis identified older age, male sex and higher CRP levels as factors associated with ILD [104].

Justification of recommendation

We suggest that patients with SjD at risk for ILD could be screened for ILD using HRCT. This recommendation is conditional due to the low certainty of evidence and the lower overall prevalence of ILD in SjD. However, not screening at-risk SjD patients with HRCT could lead to missing a significant number of ILD cases, which may increase morbidity and mortality. The risks associated with HRCT, such as radiation exposure, are minimal, and HRCT is generally preferred by patients.

Narrative question 6

Which patients with SLE should be screened for ILD?

Recommendation

Due to the lack of evidence on risk factors for ILD in SLE, the very low prevalence of ILD in SLE, and limited clinical experience, we are unable to provide a recommendation regarding which SLE patients should undergo ILD screening with HRCT.

Summary of evidence

Two observational studies [108,109] on potential risk factors for ILD in SLE included 170 patients. While these studies did not define ILD precisely, age and anti-neutrophil cytoplasmic antibodies were identified as factors associated with interstitial involvement in SLE, in one study each. However, the precise nature of these associations and their significance in relation to ILD were unclear [108,109].

Narrative question 7

How often should patients with CTD be screened for ILD?

Recommendation

Given the very low certainty of evidence for SSc, the significantly reduced incidence of ILD over the course of SSc, and the lack of evidence for other CTDs, we cannot recommend how frequently patients with CTD should be screened for ILD.

Summary of evidence

Three observational studies [13,58,61] were identified that included 1454 SSc patients. ILD at baseline was observed in 674 (46%) and 39 developed ILD over the 12-month follow-up period. One study found that ILD was detected in all patients at SSc diagnosis [13], and another study showed that only a small proportion of SSc patients developed incident ILD after negative initial screening [58]. The third study noted varying HRCT screening practices across centres [61]. No relevant evidence on screening frequency for other CTDs was demonstrated in any of the studies.

Screening algorithm

Based on the PICO questions 1–11 and narrative questions 1–7, a screening algorithm for ILD detection in CTDs based on the identification of risk factors (table 3) was developed (figure 1).

DIAGNOSIS OF ILD IN CTDS

General considerations

At the time of ILD diagnosis in patients with CTD, it is important to assess disease severity and risk of progression in order to

Table 3
Risk factors in patients with connective tissue disease and rheumatoid arthritis (RA) defining an at-risk patient population that should be screened for interstitial lung disease

	SSc	RA	IIM	SjD
Demographics	• Longer disease duration	• Older age • Male sex • Smoking	• Older age	• Older age • Male sex
Circulating markers	• Increased KL-6 • Presence of ATA-I	• Increased ESR • Presence of anti-CCP, RF	• Increased CRP, ESR • Presence of anti-Jo1, anti-MDA-5, anti-Ro52	• Increased CRP • Presence of anti-Ro52
Extrapulmonary involvement	• Diffuse cutaneous SSc • Higher mRSS	• Higher articular disease activity	• Anti-synthetase syndrome • Clinical amyopathic dermatomyositis • Skin involvement[#] • Arthritis/arthralgia	• Presence of extrapulmonary involvement

All risk factors were reported in at least two studies; risk factors reported in fewer than two studies are not included. [#]: mechanic's hands, skin ulceration, heliotrope rash. SSc: systemic sclerosis; RA: rheumatoid arthritis; IIM: idiopathic inflammatory myopathies; SjD: Sjögren disease; KL-6: Krebs von den Lungen 6; ATA-I: anti-topoisomerase I antibody; ESR: erythrocyte sedimentation rate; anti-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; CRP: C-reactive protein; anti-Jo1: anti-antihistidyl transfer RNA synthetase antibody; anti-MDA-5: anti-melanoma differentiation-associated protein 5 antibody; mRSS: modified Rodnan skin score.

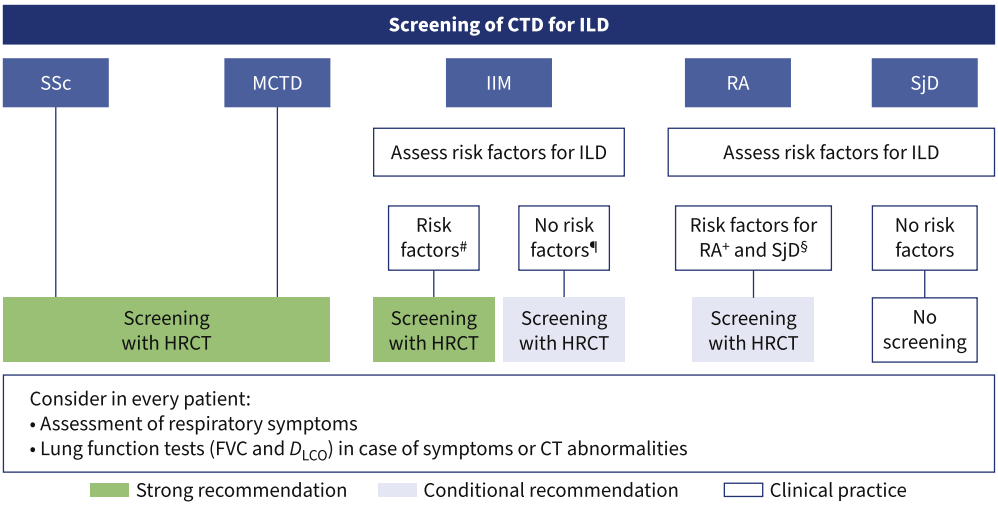

Figure 1. A screening algorithm for interstitial lung disease (ILD) detection in connective tissue disease (CTD) and rheumatoid arthritis (RA) based on the identification of risk factors. SSc: systemic sclerosis; MCTD: mixed connective tissue disease; IIM: idiopathic inflammatory myopathies; SjD: Sjögren disease; HRCT: high-resolution computed tomography; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. #: IIM: anti-synthetase syndrome, clinical amyopathic dermatomyositis, presence of mechanic's hands, arthritis, anti-synthetase, anti-melanoma differentiation-associated gene 5 and anti-Ro52 antibodies. ¶: IIM: except patients with inclusion body myositis. +: RA: older age, smoking history, elevated rheumatoid factor, anti-cyclic citrullinated peptide antibodies, increased inflammatory markers, male sex and high RA disease activity. §: SjD: older age, active extrapulmonary organ involvement and increased inflammatory markers.

individualise management. These topics were addressed in the following narrative questions.

Narrative question 8

How should patients with SSc be evaluated at baseline to assess risk of ILD progression or death?

Recommendation

We suggest performing a global assessment of all risk factors of ILD progression, including HRCT, PFTs (FVC and D_{LCO}), autoantibodies, skin involvement (extent and progression) and markers of inflammation (CRP and/or ESR) to identify SSc-ILD patients at higher risk of ILD progression and death (conditional recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

A total of 14 observational studies (n = 5268) evaluating predictive factors for ILD progression or death in SSc-ILD were included [13,61,110–121]. Progression of ILD in SSc was assessed in seven studies (n = 4085) [13,61,113–116,120] and mortality in eight studies (n = 1488) [13,110–112,117–119,121]. Factors identified as predictors of progression and/or associated with increased mortality included male sex, older age, more extensive ski fibrosis (mRSS), higher markers of inflammation (CRP, ESR), low FVC, low D_{LCO}, and more extensive ILD on HRCT. The factors most frequently associated with poor outcomes were more extensive ILD (in three studies with progression and four studies with mortality), older age (in three studies with progression and four studies with mortality), low FVC (in five studies with mortality), and low D_{LCO} (in four studies with mortality) [13,61,110–121].

Justification of recommendation

We suggest performing a global assessment for all risk factors for SSc-ILD progression to assess risk of ILD worsening or death based on the magnitude of undesirable effects if ILD progression is missed, and the negligible harms of risk evaluation. The recommendation is conditional due to the low certainty of evidence and partial data inconsistency.

Narrative question 9

How should patients with RA be evaluated at baseline to assess risk of ILD progression or death?

Recommendation

We suggest performing a global assessment of all risk factors of ILD progression, including usual interstitial pneumonia (UIP) pattern and extent of ILD on HRCT and PFTs (FVC and D_{LCO}) to identify patients with RA-ILD at higher risk of ILD progression and death (conditional recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

25, mostly cross-sectional and cohort, studies (n = 7587) [63,122–145] assessing risk factors of RA-ILD progression and death were reviewed. In eight studies (n = 1068) higher RA-ILD mortality was associated with UIP and probable UIP radiological or histopathological pattern, extent of ILD on HRCT, and lower baseline PFTs (lower FVC/D_{LCO}) [122–127,143,146]. The relationship between higher articular disease activity and ILD severity was unclear [128,129,131]. Older age at RA onset was a risk factor for RA-ILD progression in several studies [122,125–127,130,131,134,137]. Five studies [124,130,132,134,140] found that male sex was an independent risk factor for RA-ILD progression. Several biomarkers were reported as possible risk factors for RA-ILD severity, with anti-CCP and RF positivity being the most frequently associated with poor outcomes [125,132,134–136,138].

Justification of recommendation

We suggest performing a global assessment for all risk factors of RA-ILD progression to assess risk of ILD worsening or death based on the magnitude of undesirable effects if ILD progression is missed, and the negligible harms of risk evaluation. The recommendation is conditional due to the low certainty of evidence and partial data inconsistency.

Narrative question 10

How should patients with IIM be evaluated at baseline to assess risk of ILD progression or death?

Recommendation

We suggest performing a global assessment of all risk factors of ILD progression, including HRCT, PFTs (FVC and D_{LCO}) and autoantibody profile (anti-MDA-5 antibody, anti-synthetase antibodies, anti-Ro52 antibody) to identify patients with IIM-ILD at high risk of ILD progression and death (conditional recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

Among 21 cohort, cross-sectional or case–control studies (n = 1985) [147–167] regarding IIM-ILD progression, 17 were from Asia and four from Europe and the USA. The presence of anti-MDA-5 autoantibodies, high ferritin levels (>1600 ng·mL^{-1}) and higher extent of ILD and certain patterns on HRCT correlated with mortality. In anti-MDA-5-positive patients, male sex, older age, high CRP, haemophagocytic lymphohistiocytosis as part of macrophage activating syndrome, oxygen supplementation, alveolar–arterial oxygen difference and FVC <50% or inability to perform lung function tests were associated with high mortality [147–167]. Factors correlated with higher risk of rapid progressive ILD were anti-MDA-5 autoantibodies in two studies [154,165] and anti-Ro52 autoantibodies in one study [149].

Justification of recommendation

We suggest performing a global assessment for all risk factors of IIM-ILD progression to assess risk of ILD worsening or death based on the magnitude of undesirable effects if ILD progression is missed, and the negligible harms of risk evaluation. The recommendation is conditional due to the low certainty of evidence and partial data inconsistency.

Narrative question 11

How should patients with other CTDs be evaluated at baseline to assess risk of ILD progression or death?

Recommendation

Based on the very low evidence for SjD and no evidence for SLE and MCTD, we cannot make a recommendation on how patients with other CTDs should be evaluated at baseline to assess risk of ILD progression or death. It was not possible to extrapolate based on other disease entities as risk factors are disease-specific.

Summary of evidence

Only one retrospective single-centre study of patients with primary SjD and biopsy-proven ILD (n = 33) met the inclusion criteria [168].

Narrative question 12

What is the role of bronchoalveolar lavage (BAL) in patients with CTD-ILD at the time of diagnosis?

Recommendation

We suggest that BAL could have a role in patients with CTD-ILD at the time of diagnosis in cases where there is suspicion of infection or to exclude alternative diagnoses (conditional recommendation, very low certainty of evidence stemming from narrative review).

Summary of evidence

A total of 21 studies (n = 1196) [20,22,78,169–186] investigating BAL in CTD-ILD were identified, including 15 cohort studies, five case–control studies and one cross-sectional study. Patients with SSc, RA, SjD and IIM were included, and several BAL markers with contradictory results were reported. Conflicting results were reported on inflammatory cell counts or alveolitis [171,172,185,186], increased neutrophils [20,170,174,178,180,184], CD4$^+$/CD8$^+$ ratio [173], eosinophils [173,180], leukotrienes [179], and interleukin-2 and tumour necrosis factor (TNF)-α [184], and their correlation with extensive ILD. Pathogens (including *Pseudomonas aeruginosa, Haemophilus influenzae* and nontuberculous mycobacteria) were detected in the BAL fluid in 22.7% of CTD-ILD patients in one study, correlating with higher extent of pathology on HRCT and worse PFTs [181], while in another study of IIM patients, pathogens (including *Escherichia coli, Klebsiella pneumoniae*, methicillin-sensitive *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Mycobacterium tuberculosis*) were detected in BAL fluid in 24.8% (28 cases) [176].

Justification of recommendation

We suggest that BAL could play a role in patients with CTD-ILD at the time of diagnosis where there is suspicion of infection or to exclude alternative diagnoses, based on detection of pathogens in BAL and its association with worse outcomes including ILD progression in addition to other diagnostic tests to rule out differential diagnoses. The recommendation is conditional due to the low certainty of evidence and partial data inconsistency.

Narrative question 13

What is the role of lung biopsy in patients with CTD-ILD at the time of diagnosis?

Recommendation

We suggest that lung biopsy should not play a role at the time of diagnosis in patients with CTD-ILD (conditional recommendation against, very low certainty of evidence stemming from narrative review).

Summary of evidence

Two cohort studies (n = 109) [187,188] using transbronchial lung biopsy (TBLB) or surgical lung biopsy to diagnose CTD-ILD, and another study [176] using lung biopsy complementary to BAL (n = 113 in total, 23 of them underwent TBLB) were identified. One study [188] included 18 patients with SjD and suspected ILD that underwent either TBLB or surgical lung biopsy. In four patients, the diagnosis was based on TBLB results. Overall, the histological pattern was reported to correlate well with the HRCT pattern. Another study [187] included patients with unclassifiable ILD, including 91 patients with CTD-ILD in which TBLB was conducted for diagnosis. Only 13.8% (nine cases) of CTD-ILDs could be identified by TBLB. In the third study [176] including IIM patients, no clear data on the indication for biopsy, the concordance of the diagnosis with HRCT or change of diagnosis based on the findings was given. Of note, pneumothorax occurred in four patients.

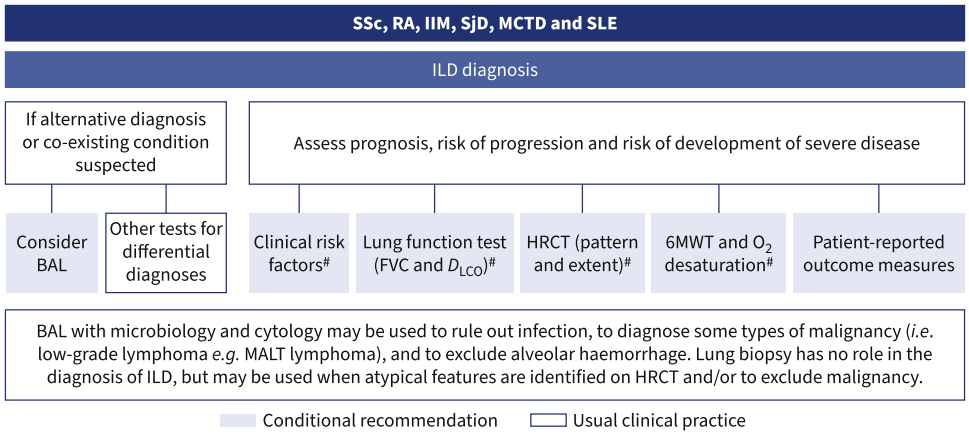

Figure 2. Work-up at diagnosis algorithm for interstitial lung disease (ILD) in connective tissue disease (CTD) and rheumatoid arthritis (RA). SSc: systemic sclerosis; IIM: idiopathic inflammatory myopathies; SjD: Sjögren disease; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; BAL: bronchoalveolar lavage; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; 6MWT: 6-min walk test; MALT lymphoma: mucosa-associated lymphoid tissue lymphoma. #: see table 4 for risk factors.

Justification of recommendation

We suggest that lung biopsy does not have a useful role in CTD-ILD at the time of diagnosis due to the potential risks and the currently lacking clear evidence of improving or affecting the diagnosis. The recommendation is conditional due to the low certainty of evidence.

Work-up at diagnosis algorithm

The algorithm for the assessment of patients at the time of diagnosis of ILD on HRCT is based on narrative questions 8–19 (figure 2 and table 4).

MONITORING OF ILD IN CTDS

General considerations

Monitoring is fundamental in the management of patients with CTD-ILD and the identification of tools and time intervals between follow-up assessments are important. These topics were addressed in the following narrative questions.

Narrative questions 14–17

What is the role of the 6-min walk test (6MWT) in assessing severity and/or prognosis of ILD in patients with SSc, RA, IIM and other CTDs?

Recommendation

We suggest using the 6MWT to assess severity and/or prognosis of ILD in patients with SSc-ILD, for RA-ILD patients with limited or no lower limb joint damage or active synovitis, for IIM-ILD without significant muscle involvement of the lower limbs and for other CTD-ILD (conditional recommendation, low certainty of evidence for SSc and very low for RA-ILD, IIM-ILD and other CTD-ILD stemming from narrative review).

Summary of evidence

We included 12 observational studies for SSc-ILD (n = 1724, 1314 of these had ILD) [120,189–199] including five prospective studies, one RCT, one systematic literature review, and one meta-analysis. In summary, weak, but statistically significant, correlations of the 6-min walk distance (6MWD) and peripheral

Table 4
Risk factors for poor outcome, defined as disease progression and death, in patients with connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

	SSc#	RA#	IIM#,¶
Demographics	• Older age • Male sex • African American ethnicity	• Older age at RA onset • Male sex	
Circulating markers	• Elevated ESR, CRP • ATA-I	• Anti-CCP, RF	• Elevated ferritin • Anti-MDA-5, anti-synthetase
Pulmonary function/markers	• Baseline PFTs (FVC, D_{LCO})	• Baseline PFTs (low FVC and/or D_{LCO})	
Imaging/histology	• Higher extent of ILD on HRCT	• UIP and probable UIP HRCT/histological patterns • Higher extent of ILD on HRCT	• Higher extent of ILD on HRCT and ILD pattern on HRCT
Extrapulmonary involvement	• Recent onset of SSc with rapid skin progression, more extensive skin fibrosis (mRSS)	• Higher articular disease activity	

All risk factors were reported in at least two studies; risk factors reported in fewer than two studies are not included. #: combination of several risk factors, such as older age and more extensive ILD on chest HRCT, have been shown to be more associated with ILD progression. As far as other CTDs are concerned, only one study regarding Sjögren disease was found, and thus not included in the table. ¶: risk factors for poor outcome in anti-MDA-5-positive IIM-ILD patients: extent of ILD on HRCT, higher ferritin levels, KL-6, older age, high P_{A-aO2}. SSc: systemic sclerosis; IMM: idiopathic inflammatory myopathies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ATA-I: anti-topoisomerase I antibody; anti-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; anti-MDA-5: anti-melanoma differentiation-associated protein 5 antibody; PFT: pulmonary function test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; mRSS: modified Rodnan skin score; KL-6: Krebs von den Lungen 6; P_{A-aO2}: alveolar to arterial oxygen tension difference.

oxygen saturation (S_{pO2}) % desaturation with PFTs (FVC and D_{LCO}) and disease progression were reported in the studies (supplementary file 2) [120,189–199]. For RA-ILD, the main body of evidence consisted of two retrospective studies (n = 416) [122,200]. Low 6MWD and S_{pO2} % desaturation were associated with worse survival and S_{pO2} % desaturation was a risk factor of acute exacerbation and acute respiratory deterioration [122,200]. For IIM, the main body of evidence consisted of two retrospective studies (n = 91, 87 of them had ILD) [201,202], where the 6MWD correlated significantly with lower FVC and D_{LCO}, but not with ILD extent on HRCT in one study, while in the other study, correlations were moderate with FVC (r = 0.66), and not existing with D_{LCO} [201,202]. For other CTD-ILDs, the body of evidence was based on three observational studies (n = 119) [192,203,204], one multicentric observational prospective study in MCTD, one CTD-ILD study that included MCTD, SjD and SLE, among others, and one bicentric study with autoimmune progressive fibrosis-ILD including SLE-ILD and MCTD-ILD. The 6MWD was lower in patients with more severe disease and a lower baseline 6MWD was a predictor of mortality in unadjusted Cox regression (HR 1.4, 95% CI 1.1 to 1.7). Post-exercise pulse increase was a risk factor for rapid progression of ILD [192,203,204].

Justification of recommendation

We suggest using the 6MWT to assess severity and/or prognosis of ILD as there is evidence that a lower 6MWD and S_{pO2} % desaturation are predictors of respiratory deterioration and progression in patients with SSc-ILD, and predictors of mortality, acute respiratory deterioration and acute exacerbation in RA-ILD patients, and as the 6MWD correlated with lung function in IIM-ILD and as lower 6MWD was associated with ILD severity and worse prognosis in patients with other CTD-ILD. The recommendation is conditional due to the low certainty of evidence for SSc-ILD and very low for RA-ILD, IIM-ILD and other CTD-ILD, and there were some concerns on applicability in certain patient subgroups

Narrative questions 18 and 19

What is the role of patient-reported outcome measures (PROMs) in assessing severity and/or prognosis of ILD in patients with SSc-ILD and in patients with any CTD-ILD other than SSc-ILD?

Recommendation

We suggest using PROMs to evaluate symptom and disease burden and patient needs in order to assess severity of ILD in patients with SSc-ILD, RA-ILD, IIM-ILD and other CTD-ILD (conditional recommendation, low certainty of evidence for SSc and very low certainty of evidence stemming from narrative review).

Summary of evidence

The main body of evidence for SSc consisted of six studies (n = 1268, including 1164 with ILD) [190,205–209], three observational studies and three RCTs where PROMs were included as secondary outcome. All studies used one or more PROMs, including Mahler Transition Dyspnoea Index (TDI) [210], Leicester Cough Questionnaire (LCQ) [211], St George's Respiratory Questionnaire (SGRQ) [212], Functional Assessment of Chronic Illness Therapy (FACIT)-dyspnoea scale [213], Visual Analogue Scale (VAS) for breathing [214], King's Brief Interstitial Lung Disease (K-BILD) questionnaire [215], Medical Research Council (MRC) scale [216], and Health Assessment Questionnaire – Disability Index (HAQ-DI) [217]. PROMs (or components of PROMs) correlated not or weakly with HRCT and PFTs [190,205–209]. One study showed statistically significant correlations of respiratory PROMs with FVC <70% and HRCT extent ≥30%, but they were not confirmed in longitudinal analysis [208]. Two studies reported [205,209] statistically significant correlations of respiratory PROMs with FVC and D_{LCO}, and one with 6MWD [190]. The main body of evidence for all other diseases, including RA, IIM and other CTDs, consisted of three studies (n = 428, 402 of them had ILD) [218–220], two observational studies and one RCT where PROMs were included as a secondary outcome. All studies used one or more tools, including Living with Pulmonary Fibrosis questionnaire [221], LCQ [211], SGRQ [212], VAS for breathing [214], Modified Borg Scale [222] and MRC scale [216]. PROMs correlated not or weakly with HRCT and PFTs [218–220]. Statistically significant correlations with FVC, D_{LCO}, 6MWT and S_{pO2}, and associations with mortality were found in one study [218]. Statistically significant correlation was observed only for SGRQ with the Warrick score (r = 0.531, p = 0.028), but no significant correlations of any PROM with PFTs were reported [220].

Justification of recommendation

We suggest using PROMs to evaluate symptom and disease burden and patient needs in order to assess severity of ILD in patients with SSc-ILD, RA-ILD, IIM-ILD and other CTD-ILD, as PROMs correlate with other severity assessment tools, are non-invasive and complement patient-centred domains in the severity assessment. The recommendation is conditional due to the low certainty of evidence for SSc-ILD and very low for all other CTD-ILDs, heterogeneity in the results, the use of various PROMs and the lack of data on associations with worse prognosis.

Narrative question 20

In patients with SSc-ILD being followed-up, when should PFTs be repeated?

Recommendation

We suggest repeating PFTs (FVC and D_{LCO}) every 3–6 months during the first 3–5 years for follow-up in patients with SSc-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, low certainty of evidence stemming from narrative review).

Summary of evidence

The body of evidence consisted of 47 studies (n = 5386), mostly retrospective other than two prospective studies and 10 RCTs [13,14,57,58,110,112,113,116,118,120,206,223–258]. In most studies, FVC and D_{LCO} were performed. FVC was shown to be more responsive to treatment than D_{LCO}. In the retrospective studies, the changes in FVC or D_{LCO} were significantly correlated with mortality. We did not identify direct evidence for the optimal frequency of PFTs. In recent RCTs [232,256,258,259], FVC was performed at least every 3 months over the study period of 1 year.

Justification of recommendation

We suggest repeating PFTs (FVC and D_{LCO}) every 3–6 months during the first 3–5 years for follow-up in patients with SSc-ILD, and at least every 6–12 months thereafter, based on correlations between changes in FVC and D_{LCO} and responsiveness to treatment and mortality. The recommendation is

conditional due to the low certainty of evidence and some uncertainty about the exact frequency of repetition.

Narrative question 21

In patients with RA-ILD being followed-up, when should PFTs be repeated?

Recommendation

We suggest repeating PFTs (FVC, D_{LCO} and forced expiratory volume in 1 s (FEV_1) in view of the possible concomitant airway component) every 3–6 months during the first 1–2 years for follow-up in patients with RA-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).

Summary of evidence

The main body of evidence consisted of 16 studies (n = 1717), including 13 cohort studies, one non-randomised prospective trial and two RCTs [123,132,133,143,145,260–270]. In nine studies, the frequency of PFTs was specified to be every 3 months in two prospective studies, every 6 months in four studies, 12 months in two studies, and 2 years in one prospective study. FVC changes were reported in 16 studies and D_{LCO} changes in 11 studies. The data from these studies indicated that FVC or D_{LCO} decline was associated with a worse prognosis with increased risk of death [123,132,133,143,145,260–270].

Justification of recommendation

We suggest repeating PFTs (FVC and D_{LCO}) every 3–6 months during the first 1–2 years for follow-up in patients with RA-ILD, and at least every 6–12 months thereafter, due to associations between changes in FVC and D_{LCO} and death. The recommendation is conditional due to the very low certainty of evidence and some uncertainty about the exact frequency of repetition.

Narrative question 22

In patients with IIM-ILD being followed-up, when should PFTs be repeated?

Recommendation

We suggest performing PFTs (FVC and D_{LCO}) every 3–6 months during the first year for follow-up in patients with IIM-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).

Summary of evidence

The main body of evidence consisted of 16 studies (n = 1176) [242–244,258,271–282], mostly assessing treatment response. The follow-up PFT intervals most often used were 0, 1, 3, 6 and 12 months. FVC was used more often than other measures, including D_{LCO}. FVC started to demonstrate significant changes at 3 months in most studies; in rapidly progressive ILD also at 1 month. In a few studies D_{LCO} started to show significant changes at 3 months, yet overall, was less reliable compared to FVC.

Justification of recommendation

We suggest performing PFTs (FVC and D_{LCO}) every 3–6 months during the first year for follow-up in patients with IIM-ILD, and at least every 6–12 months thereafter, due to associations between changes in FVC and D_{LCO} with ILD progression and treatment response. The recommendation is conditional due to the very low certainty of evidence and some uncertainty about the exact frequency of repetition.

Narrative question 23

In patients with other CTD-ILD being followed-up, when should PFTs be repeated?

Recommendation

We suggest performing PFTs (FVC, D_{LCO} and FEV_1 in view of the possible concomitant airway component) every 3–6 months during the first year for follow-up in patients with SjD-ILD, and at least every 6–12 months thereafter, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review). No recommendation could be made for SLE and MCTD due to absence of evidence.

Summary of evidence

We included one retrospective study (n = 19), which assessed treatment response. The slope of D_{LCO} % and FVC % differed significantly already in the first months based on the response to treatment [283].

Justification of recommendation

We suggest performing PFTs (FVC and D_{LCO}, and FEV_1 in view of the possible concomitant airway component) every 3–6 months during the first year for follow-up in patients with SjD-ILD, and at least every 6–12 months thereafter, due to the association of changes in FVC and D_{LCO} with treatment response. This is a conditional recommendation due to very low certainty of evidence and lack of data on associations with worse prognosis.

Narrative question 24

In patients with SSc-ILD being followed-up, when should HRCT be repeated?

Recommendation

We suggest regularly repeating HRCT after 1–2 years in patients with SSc-ILD, particularly in those at higher risk of progression and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).

Summary of evidence

The main body of evidence consisted of 24 studies (n = 4594) [13,14,57,58,110,113,116,118,223–238]. There was no direct evidence for the optimal frequency of HRCT in these studies. In some trials [232,256,259], HRCT was performed at baseline and repeated after 1 or 2 years. Quantitative measures of HRCT evaluation were found to be sensitive to change reflecting treatment response or progression, and ILD progression on HRCT was correlated with reduced survival [226,233,234,238].

Justification of recommendation

We suggest repeating HRCT after 1–2 years, particularly in patients at higher risk of progression and in case of suspected

progression, due to change of HRCT findings reflecting treatment response or ILD progression correlating with reduced survival. The recommendation is conditional due to the very low certainty of evidence and some uncertainty over the exact interval of repeating HRCTs.

Narrative question 25

In patients with RA-ILD being followed-up, when should HRCT be repeated?

Recommendation

We suggest regularly repeating HRCT after 1–2 years in patients with RA-ILD, particularly in those at higher risk of progression and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).

Summary of evidence

The main body of evidence was consisted of 16 studies (n = 1717), but without direct evidence for the optimal frequency of HRCT assessments in these studies [123,132,133,143,145,260–270]. HRCT was obtained after 1 year in two prospective studies [264,265], after 2 years in one prospective study [261], in case of symptoms in one study [260], after a median follow-up of 4 years in another study [133], and annually for more than 3 years in another study [263]. Data concerning HRCT changes were given in three studies only [133,260,261]. One study assessed HRCT findings in a small number of patients with worsening dyspnoea and/or lung function, and identified that 50% also worsened on imaging [260]. The progression of ILD extent on HRCT varied between 27% and 38% in two studies [133,261].

Justification of recommendation

We suggest repeating HRCT after 1–2 years in patients with RA-ILD due to correlations between other severity assessment tools and changes on HRCT and indirect evidence of associations of changes on HRCT with worse outcome. The recommendation is conditional due to the very low certainty of evidence, some uncertainty over the exact frequency of repeat HRCTs and the lack of data on associations with worse prognosis.

Narrative question 26

In patients with IIM-ILD being followed-up, when should HRCT be repeated?

Recommendation

We suggest repeating HRCT after 3–6 months in patients at risk of developing severe or rapidly progressive IIM-ILD, annually over the first 2 years, and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).

Summary of evidence

The main body of evidence consisted of 13 studies (n = 596) [271,273,275–282,284–286], with most assessing treatment response. The HRCT intervals varied widely. In rapidly progressive ILD, the intervals were between 1 and 3 months. For others, HRCT was repeated at 6–12 months or in case of suspicion of relapse/disease worsening. Quantitative, but not visual measures were sensitive to change. In several studies treatment efficacy correlated with improvement of HRCT findings [271,273,275–282,284–286].

Justification of recommendation

We suggest repeating HRCT in patients with IIM-ILD depending on severity and risk of progression due to correlations between treatment response and changes on HRCT and indirect evidence of associations with worse outcomes. This is a conditional recommendation due to the very low certainty of evidence, uncertainty in the intervals of repeating HRCT, selected patient populations and the lack of data on associations with worse prognosis.

Narrative question 27

In patients with other CTD-ILD being followed-up, when should HRCT be repeated?

Recommendation

We suggest repeating HRCT after 1–2 years in patients with other CTD-ILD, particularly in those at higher risk of progression and in case of suspected progression (conditional recommendation, very low certainty of evidence stemming from narrative review).

Summary of evidence

There is no direct evidence to determine the optimal time intervals for repeating HRCT in other CTD-ILD. There is only indirect evidence from studies regarding other disease entities as described above.

Justification of recommendation

We suggest repeating HRCT after 1–2 years in patients with other CTD-ILD due to indirect evidence of associations of changes on HRCT with worse outcome. This is a conditional recommendation due to very low certainty of evidence and uncertainties due to the indirect evidence from SSc, RA and IIM-ILDs for repeating HRCT.

Monitoring algorithm

The monitoring algorithms are based on narrative questions 14–27 (figure 3a–d).

TREATMENT OF ILD IN CTDS

General considerations

Treatment considerations are important to prevent disease progression and improve symptoms, quality of life and survival. To address these issues in our treatment PICO questions, we focused on critical outcomes including FVC, D_{LCO} and mortality, and important outcomes, including extrapulmonary manifestations, health-related quality of life (HRQoL), symptom burden, hospital admissions (respiratory related and all cause), lung transplant and adverse events (including infection). These outcomes were assessed for every PICO regarding treatment. Key factors in patient selection for specific treatment options were addressed in the relevant questions. Details are found in supplementary file 2.

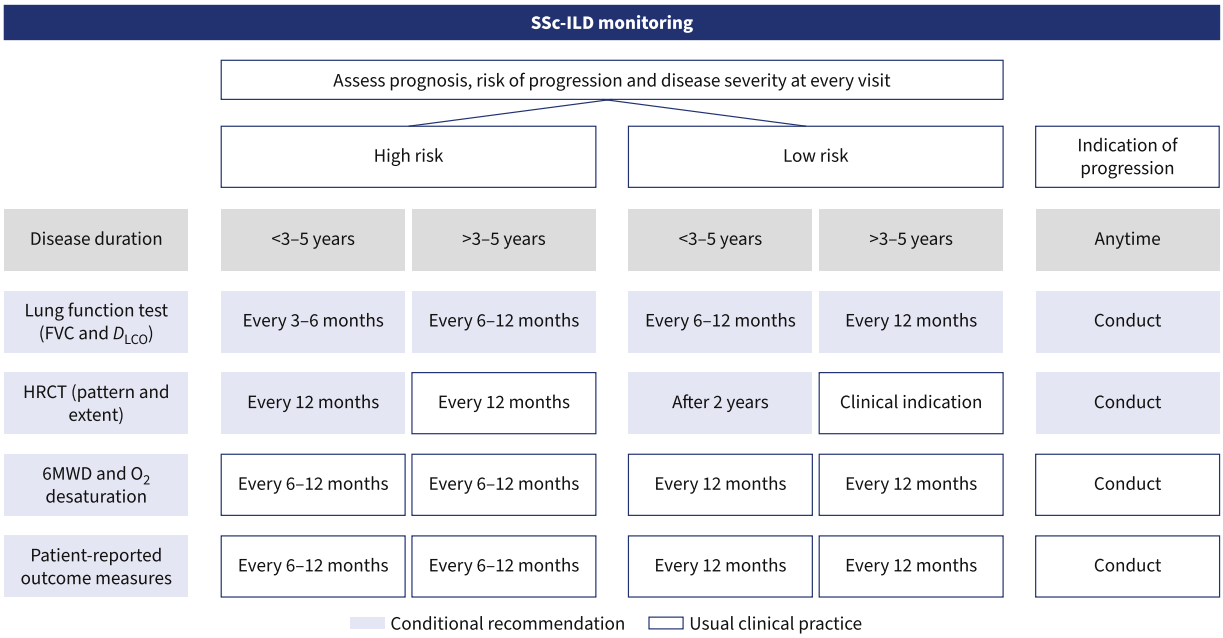

Figure 3a. Monitoring approach for patients with systemic sclerosis (SSc)-associated interstitial lung disease (ILD). FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; 6MWD: 6-min walk distance.

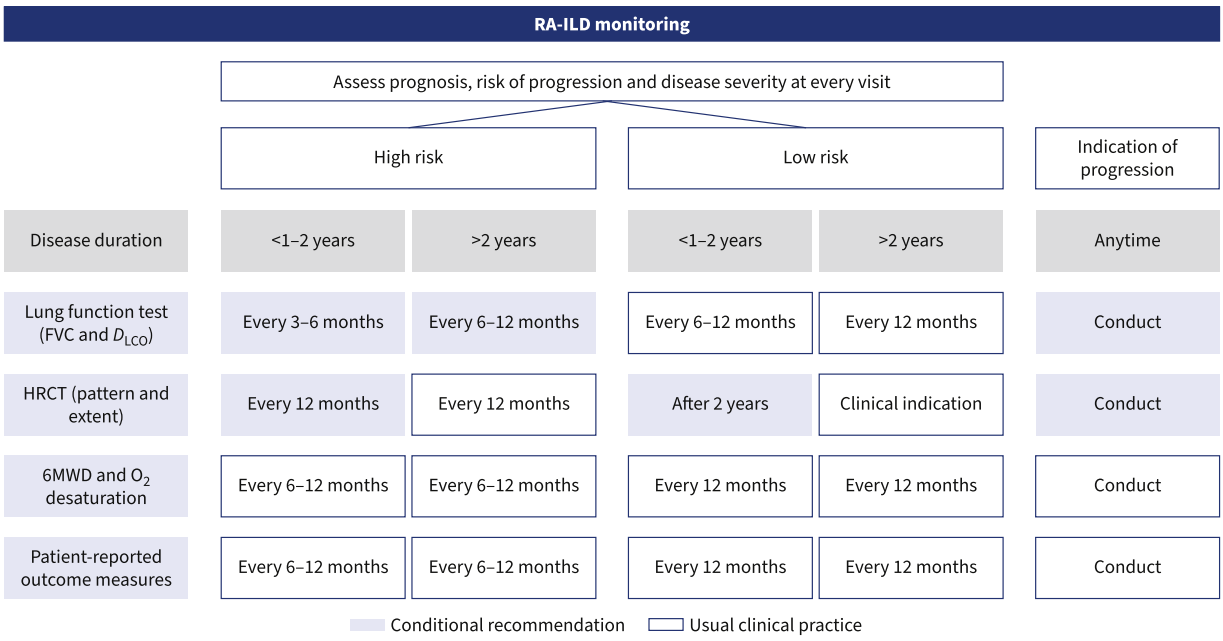

Figure 3b. Monitoring approach for patients with rheumatoid arthritis (RA)-associated interstitial lung disease (ILD). FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; 6MWD: 6-min walk distance.

PICO question 12

Should mycophenolate mofetil (MMF) *versus* control be used for patients with SSc-ILD?

Recommendation

We suggest using MMF in patients with SSc-ILD (conditional recommendation, very low certainty of evidence).

Summary of evidence

We included two RCTs; comparing MMF either with placebo for 6 months (n = 42) (MYILD) [287] or with cyclophosphamide over 2 years (n = 142) (SLS-II) [256]. As the comparators differed, the data could not be pooled. No deaths were reported in either arm of MMF and placebo [287]. One death occurred in the MMF group and none in the cyclophosphamide group [256]. The mean absolute FVC % predicted difference favoured MMF over placebo at 6 months (mean difference (MD) 3.1%, 95% CI −1.0 to 7.3). While there was no significant MD in FVC % predicted in the MMF group compared to cyclophosphamide (MD −0.69%, 95% CI −3.1 to 1.72), there was an improvement of FVC in MMF (MD 2.19%, 95% CI 0.53−3.84), with 71.7% showing improved FVC. D_{LCO} % predicted did not show significant differences in either study. MMF demonstrated a significant reduction in mRSS compared to placebo (MD −3.2%), while compared to cyclophosphamide mRSS improved in both treatment arms, with no difference between the groups (MD 0.45, 95% CI −1.7 to 2.6). MMF treated patients showed comparable changes in HRQoL and dyspnoea as placebo or cyclophosphamide. No changes were seen on HRCT in either of the studies. A

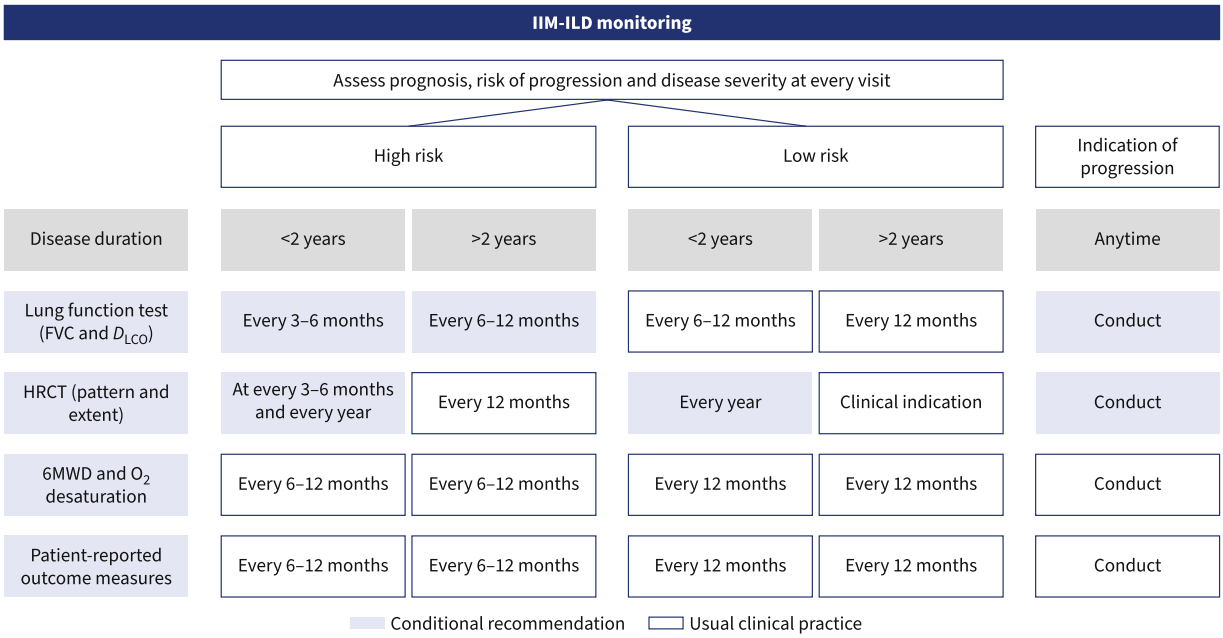

Figure 3c. Monitoring approach for patients with interstitial lung disease (ILD) associated with idiopathic inflammatory myopathies (IIM). FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; 6MWD: 6-min walk distance.

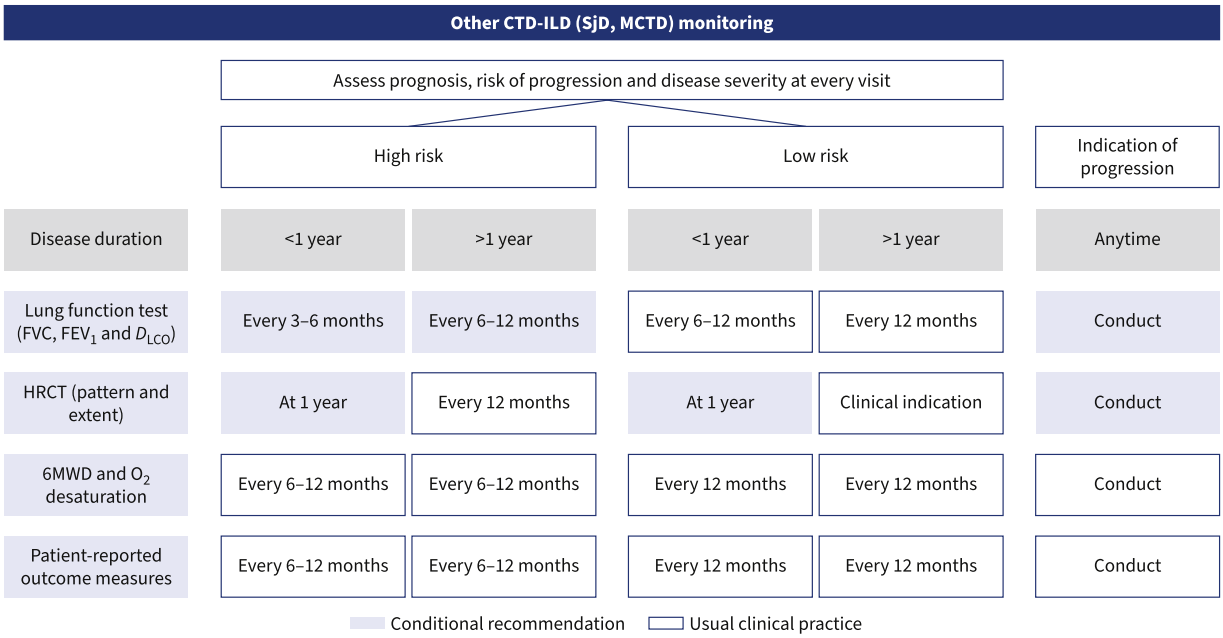

Figure 3d. Monitoring approach for patients with interstitial lung disease (ILD) associated with Sjögren disease (SjD) and mixed connective tissue disease (MCTD). CTD: connective tissue disease; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; 6MWD: 6-min walk distance.

small but significant improvement in quantitative ILD (QILD) score was seen after 24 months for both MMF (MD −2.51, 95% CI −4.9 to −0.15) and cyclophosphamide (MD −2.78, 95% CI −5.17 to −0.40). Adverse events were more frequently reported with MMF compared with placebo, and numerically more frequently with cyclophosphamide than MMF. There was serious risk of bias and very serious imprecision and the overall certainty of evidence was very low.

Indirect evidence

Sub- and *post hoc* analyses of the SLS-II support the efficacy of MMF [230,288–291]. In a *post hoc* analysis of the SENSCIS study, in which MMF was used as background therapy in 49% of the study population, the adjusted annual rates of FVC decline were 66.5 mL with MMF (SD 19.3), and 119.3 mL without MMF (SD 19.0). While MMF was associated with more adverse events compared with placebo, including gastrointestinal symptoms and reduced vaccination response, fewer patients experienced serious adverse events [287].

Justification of recommendation

We suggest using MMF in patients with SSc-ILD, as the included studies suggested improvement or stabilisation of FVC % and the extent of ILD on HRCT, improvement of breathlessness, cough and quality of life, and improved skin scores with manageable side-effects. The recommendation is conditional

based on the very low certainty of evidence due to risk of bias and imprecision and the lack of data on other important outcomes.

PICO question 13

Should tocilizumab *versus* control be used for patients with SSc-ILD?

Recommendation

We recommend using tocilizumab in SSc-ILD patients with early diffuse cutaneous SSc and increased inflammatory markers or recent skin fibrosis progression (strong recommendation, moderate certainty of evidence).

Remark

The effect of tocilizumab has only been studied in a specific subgroup of SSc patients and the recommendation is therefore restricted to inflammatory, diffuse cutaneous, early, skin progressive SSc-ILD patients.

Summary of evidence

We included two RCTs; one phase 2 trial (n = 77) (faSScinate) [248] and one phase 3 trial (n = 210) (focuSSced) [232]. Both compared tocilizumab with placebo over 48 weeks in inflammatory, diffuse cutaneous, early, skin progressive SSc-ILD patients. When assessing the same outcomes, data were pooled, and a meta-analysis performed. The mortality rate for weekly tocilizumab *versus* placebo was 2.7% in both groups (RR 1.03, 95% CI 0.12 to 8.88). The MD in FVC % (4.06%, 95% CI 2.19 to 5.94), mRSS (2.2 points, 95% CI −4.11 to −0.29), and fatigue reduction (2.56, 95% CI 0.48 to 4.65) favoured tocilizumab over placebo, while similar counts of tender joints were observed and no differences in Scleroderma Health Assessment Questionnaire VAS and patient global VAS scores were identified (MD −0.09, 95% CI −0.22 to 0.04). Tocilizumab demonstrated greater improvement in respiratory symptom burden (MD −2.1, 95% CI −6.0 to 1.7). Exploratory analysis of the trial revealed numerical improvements in quantitative lung fibrosis and QILD scores with tocilizumab. Weekly tocilizumab had a higher proportion of adverse events compared with placebo (89.1% *versus* 81.3%; RR of 1.09, 95% CI 1.00 to 1.18). There was very serious imprecision in at least one of the critical outcomes and the overall certainty of evidence was low.

Indirect evidence

In a multicentre, real-life observational study (EUSTAR cohort) [292], tocilizumab did not show significant effectiveness. However, consistent trends in predefined end-points, including mRSS and FVC at 12±3 months, suggested a potential effectiveness in a broader SSc population compared to the specific populations from the assessed randomised trials. The two open-label extension studies (focuSSced and faSScinate) [293,294] demonstrated FVC stabilisation over time with tocilizumab. Specifically, the phase 3 extension study showed a reduction in mRSS and a modest change in FVC % predicted with 0.9 (95% CI −0.8 to 2.7) for placebo-tocilizumab and −0.4 (95% CI −2.3 to 1.5) for continuous-tocilizumab; rates of serious adverse events were comparable between groups.

Justification of recommendation

We recommend using tocilizumab for patients with SSc-ILD who have early diffuse cutaneous SSc, elevated inflammatory markers, or recent progression of skin fibrosis. Tocilizumab has shown efficacy in stabilising FVC, improving extrapulmonary manifestations such as skin fibrosis and fatigue, with a tolerable side-effect profile. The certainty of evidence is moderate based on imprecision. However, the recommendation is strong based on the significant stabilisation of FVC in the tocilizumab group compared to marked progression in the placebo group. These benefits outweigh the risks in this population, which has a high probability for severe and rapidly progressing ILD.

PICO question 14

Should rituximab *versus* control be used for patients with SSc-ILD?

Recommendation

We suggest using rituximab in patients with SSc-ILD (conditional recommendation, very low certainty of evidence).

Summary of evidence

We included two RCTs; one comparing rituximab (four doses of weekly *i.v.* rituximab) with placebo at 24 weeks (n = 56) (DESIRES) [295] and one comparing rituximab with cyclophosphamide (*i.v.* rituximab *versus* monthly *i.v.* cyclophosphamide) (n = 60) [296]. As the comparators differed, the data could not be pooled. In the study comparing rituximab with placebo, no deaths were recorded. In the comparison between rituximab and cyclophosphamide, the mortality rate was 1 out of 30 (3.3%) in both groups. FVC % predicted showed a MD of 2.96% (95% CI 0.08 to 5.84) for rituximab *versus* placebo and an MD of 9.46% (95% CI 3.15 to 15.77) *versus* cyclophosphamide. D_{LCO} % predicted had an MD of 2.24% (95% CI −2.47 to 6.94) for rituximab *versus* placebo. Extrapulmonary organ manifestations, assessed by mRSS, showed improvement in both studies (MD of −6.23, 95% CI −10.78 to −1.68, and −8.44, 95% CI −11.00 to −5.88) *versus* cyclophosphamide and placebo). Quality of life, measured by the HAQ-DI, showed improvement compared to placebo (MD −0.03, 95%CI −0.20 to 0.15). One patient in the cyclophosphamide group required hospitalisation for pneumonia, but none in the rituximab group. Fewer adverse events occurred with rituximab compared with cyclophosphamide (OR 0.18, 95% CI 0.06 to 0.55). All patients in the rituximab group, and 88% in the placebo group, reported at least one adverse event, with upper respiratory tract infections being the most common. There was serious risk of bias and very serious imprecision in at least one of the critical outcomes. The overall certainty of evidence was very low.

Indirect evidence

Rituximab demonstrated superiority over cyclophosphamide in improving the 6MWD (60.46 m; p = 0.001) and reducing disease activity assessed by the Medsger severity scale (−1.3; p = 0.036) [296]. A small 24-month trial in early SSc patients showed no significant difference in mRSS between rituximab and placebo, with slight but insignificant improvements in FVC and lung involvement on HRCT with rituximab [297]. Other non-randomised studies reported beneficial effects on lung function and skin involvement, while others did not [229,298]. In a prospective study involving 51 SSc-ILD patients [299], rituximab treatment was associated with improved FVC and mRSS. In the RECITAL study including SSc-ILD patients [258], rituximab was found to be as effective as cyclophosphamide on FVC, improving HRQoL and physician-assessed global disease activity scores. The EVER-ILD trial [300] demonstrated a positive impact of rituximab plus MMF on FVC % predicted compared to placebo

plus MMF in the total study population, including CTD-ILD patients. Adverse and serious adverse events were not significantly higher in the rituximab group compared to placebo [297]. In the RECITAL trial [258], compared with cyclophosphamide, rituximab treatment showed fewer adverse events. In the EVER-ILD trial [300], serious adverse events were comparable between groups, but rituximab and MMF patients had more infections. There are concerns about reduced vaccine responses and worse disease courses in rituximab-treated patients [300].

Justification of recommendation

We suggest using rituximab in SSc-ILD as it resulted in improvement or stabilisation of FVC % and treatment efficacy on the skin, with cumulative indirect evidence from other studies with manageable side-effects. The recommendation is conditional due to the very low certainty of evidence based on risk of bias and imprecision and the lack of data on other important outcomes.

PICO question 15

Should cyclophosphamide *versus* control be used for patients with SSc-ILD?

Recommendation

We suggest using cyclophosphamide in patients with SSc-ILD (conditional recommendation, low certainty of evidence).

Summary of evidence

We included two RCTs, one evaluating efficacy of oral cyclophosphamide against placebo in 158 patients with SSc-ILD (SLS-I) [259], and one comparing *i.v.* cyclophosphamide for 6 months in combination with 20 mg prednisone on alternate days, followed by azathioprine, compared to placebo in patients with SSc-ILD (n = 37) (FAST) [247]. Data were not pooled due to the different route of administration. In the study assessing *i.v.* cyclophosphamide, the mortality rates were 4.5% and 0.0%, respectively. Oral cyclophosphamide was associated with mortality rates of 2.5% compared to 3.8% for placebo. Compared to placebo, the adjusted mean relative effect on FVC % predicted was 4.19% (95% CI −0.57 to 8.95) for *i.v.* cyclophosphamide, while the adjusted mean absolute difference was 1.95% (95% CI 1.2 to 2.6) for oral cyclophosphamide. Patients receiving oral cyclophosphamide reported improved HRQoL *versus* placebo for both the physical (0.7±1.0 *versus* −1.9±1.2) and the mental component (2.9±1.5 *versus* 0.1±1.5) of the 36-Item Short Form Survey (SF-36). No significant differences were found in dyspnoea assessed by the modified American Thoracic Society questionnaire, but the Mahler TDI showed a clinically meaningful improvement in the cyclophosphamide group (+1.4±0.23) *versus* worsening in the placebo group (−1.5±0.43). Cyclophosphamide led to significant improvements in mRSS compared to placebo, with a mean improvement of 3.6±0.8 points *versus* worsening of −0.9±1.2 in the placebo group ($p<0.05$). Adverse events were more frequent in cyclophosphamide-treated patients, including leukopenia, neutropenia, anaemia, pneumonia and nausea. There was very serious imprecision in at least one of the critical outcomes and the overall certainty of evidence was low.

Indirect evidence

In the SLS-I trial, patients were followed until 1 year after treatment cessation (2 years after start) and effects on lung function, skin scores, dyspnoea and health status persisted or improved further for several months after treatment cessation. However, these effects disappeared at 24 months [255]. The efficacy of cyclophosphamide was comparable to MMF in the SLS-II trial, with significant improvements compared to baseline in FVC, SGRQ, mRSS and QILD score at 24 months [230,256,288–290]. In *post hoc* analyses, dyspnoea and cough-related quality of life were also improved [230,288,289]. Multiple small non-randomised studies analysed the effect of cyclophosphamide on different outcomes in SSc-ILD, with conflicting results [301]. A randomised trial comparing cyclophosphamide and rituximab showed that both drugs improved lung function, with cyclophosphamide associated with a significant improvement in skin [296]. In the RECITAL study, cyclophosphamide was as efficacious as rituximab in SSc-ILD patients [258].

Justification of recommendation

We suggest using cyclophosphamide in SSc-ILD as it resulted in improvement or stabilisation of FVC %, extent of ILD on imaging, improvement of breathlessness, cough and quality of life, and had a treatment benefit on the skin. The recommendation is conditional due to the low certainty of evidence based on imprecision, and some concerns about side-effects and the limited treatment duration due to cumulative toxicity.

PICO question 16

Should immunosuppressive treatment *versus* control be used for patients with IIM-ILD?

Recommendation

We recommend using immunosuppressive treatment in patients with IIM-ILD (strong recommendation, very low certainty of evidence).

Summary of evidence

We included one RCT comparing tacrolimus with cyclosporin A [274] and four observational studies comparing intravenous immunoglobulin (IVIG) *versus* no IVIG, cyclophosphamide compared to rituximab, tacrolimus *versus* no tacrolimus, and glucocorticoids and calcineurin inhibitor compared to glucocorticoids [302–305]. Due to the different immunosuppressive agents with different mode of action, data could not be pooled. Significant differences existed in mortality rates between treatment groups (4.2–23% and 20–53% in IVIG or tacrolimus compared to no IVIG or no tacrolimus). FVC % predicted improved by 9% and 10% in patients treated with tacrolimus compared to cyclosporin A. D_{LCO} improved by 14.7% in cyclophosphamide- and by 9.7% in rituximab-treated patients ($p = 0.39$). Extrapulmonary manifestations (muscle involvement) improved in manual muscle testing and creatine kinase levels in tacrolimus compared to no tacrolimus, without reported direct comparison. Imaging changes on HRCT improved in cyclophosphamide- compared to rituximab-treated patients and in IVIG compared to no IVIG, without direct comparison. New York Heart Association class improved from 3 to 2 for cyclophosphamide and from 3 to 1.5 for rituximab, without direct comparison. Serious adverse events were seen in 30% for tacrolimus and 10.7% for cyclosporin A treatment ($p = 0.30$). No significant differences in adverse events were identified in the studies. There was serious risk of bias and very serious imprecision in all outcomes, and the overall certainty of evidence was very low.

Indirect evidence

Indirect evidence from various, mostly small, retrospective studies without comparator, underscores the efficacy of immunosuppressive agents in treating IIM-ILD [278,279,303,306,307]. Cyclosporin A treatment significantly improved survival rates, particularly with early initiation (6.3% *versus* 45.2%; p = 0.009) [303]. Tacrolimus and glucocorticoids as initial therapy demonstrated improved short-term mortality compared with historical controls (88% 52-week survival) [278]. Patients with anti-MDA-5 autoantibody treated with upfront combined immunosuppressants showed significantly improved survival compared with those treated with a step-up approach (89% *versus* 33% and 85% *versus* 33%; p<0.000) [279]. Upfront immunosuppression led to better survival outcomes compared with delayed initiation (p = 0.03 for 12-month survival) [307]. The RECITAL study [258] demonstrated improvement in FVC with both *i.v.* cyclophosphamide and rituximab treatment. IVIG treatment was also associated with significant improvement in FVC % and D_{LCO} % in refractory disease [308]. Patients with initial use of cyclophosphamide, MMF and azathioprine showed no significant difference in outcomes at 6 months with all groups experiencing a slight improvement in FVC and dyspnoea [309]. IVIG has shown efficacy in dermatomyositis [310], but its impact on ILD remains little explored. Rapidly progressive ILD in IIM requires intensive treatment for improved survival, with rituximab showing efficacy in small uncontrolled studies [311].

Justification of recommendation

We recommend using immunosuppressive therapy (including glucocorticoids) for patients with IIM-ILD, as it has been shown to improve survival, lung function, ILD extent, breathlessness and extrapulmonary organ involvement, with an acceptable safety profile. This strong recommendation is made despite the very low certainty of evidence based on risk of bias and imprecision, due to the narrow treatment window for this frequently severe and rapidly progressing disease, which is associated with high intensive care unit admission rates. Immunosuppressive treatment has demonstrated improvements in both survival and lung function. Prompt intervention with immunosuppression should be considered for IIM-ILD patients, with the choice of agents tailored to each patient based on the severity and progression of their ILD.

PICO question 17

Should immunosuppressive treatment *versus* control be used for patients with RA-ILD?

Recommendation

We suggest using immunosuppressive treatment in patients with RA-ILD (conditional recommendation, very low certainty of evidence).

Summary of evidence

The summary of evidence is based on three observational studies [137,312,313], assessing methotrexate compared to no methotrexate, rituximab compared to no rituximab and Janus-kinase inhibitor (JAKi) compared to abatacept. Due to the different immunosuppressive agents and different mode of action, data could not be pooled. In one study [137] assessing mortality rates, lower mortality was identified in the methotrexate group (HR 0.063, 95% CI 0.15 to 0.47). No significant changes in FVC % and D_{LCO} % predicted were identified in patients on rituximab or JAKi compared to no rituximab or abatacept [312,313]. HRQoL, assessed by HAQ-DI, improved with both JAKi and abatacept treatments. Both JAKi and abatacept treatments resulted in improvements of extrapulmonary manifestations assessed by Clinical Disease Activity Index. Imaging assessments showed no significant change in fibrosis scores. The Borg scale improved with both JAKi and abatacept treatments. Regarding adverse events, two patients in the rituximab group experienced adverse events, while the number of adverse events in the non-rituximab group was not reported. There was serious risk of bias and very serious imprecision in all outcomes, and the overall certainty of evidence was very low.

Indirect evidence

Several non-controlled retrospective studies have provided indirect evidence, with improvement in survival rates for treatments such as cyclophosphamide (HR 0.43) and methotrexate (HR 0.58) [314]. Mortality risk varied among treatments, with longer survival observed in patients treated with rituximab used as their first biologic treatment [315]. Treatment with rituximab also resulted in lower mortality rates compared to TNF inhibitor (TNFi) in RA-ILD patients [316]. FVC improvements were noted in RA-ILD patients receiving rituximab compared with other treatments [269]. Abatacept treatment showed stable or increased FVC in the majority of patients [317], while tocilizumab led to FVC stabilisation or improvement in some cases [318]. D_{LCO} remained stable or increased with abatacept treatment [317], tocilizumab showed mixed results, and other treatments such as azathioprine, MMF and rituximab demonstrated D_{LCO} improvement compared with the potential 12-month response without treatment [145]. HRCT findings remained stable or improved with abatacept and tocilizumab treatments [317,318], while anti-TNF treatment showed more ILD progression on HRCT [319]. Uncontrolled articular disease and FVC impairment were associated with increased mortality risk, emphasising the importance of optimised RA disease management [128]. Abatacept treatment showed efficacy in achieving remission or low disease activity in RA patients and improved dyspnoea [317,320]. A systematic review has shown the efficacy of cyclophosphamide and azathioprine on articular disease [321,322]. Limited data exist regarding the adverse events from immunosuppression in RA-ILD. Acute pneumonitis has been reported with several drugs, including methotrexate and TNFi, which has been a concern in clinical practice. More recent studies have, however, shown improved survival without increased incidence of ILD in methotrexate-treated patients [137,323]. Abatacept was discontinued in 62 (23.6%) patients due to adverse events or articular inefficacy [320]. A literature review including nine studies did not reveal unexpected adverse events [324]. Regarding infections, the highest rate occurred with daily prednisone use >10 mg·day^{-1}, with no significant differences observed in serious infection rates between various treatment regimens [325].

Justification of recommendation

We suggest using immunosuppressive treatment in RA-ILD as it resulted in stabilisation of lung function and extent of lung fibrosis, and improvement in dyspnoea, quality of life and arthritis, with an acceptable adverse event profile. The recommendation is conditional based on the very low certainty of evidence based on risk of bias and imprecision.

PICO question 18

Should immunosuppressive treatment *versus* control be used for patients with other CTD-ILD?

Recommendation

We suggest using immunosuppressive treatment in patients with SjD, MCTD and SLE-ILD (conditional recommendation, very low certainty of evidence; no studies included).

Summary of evidence

We did not identify any studies using a comparator addressing the use of immunosuppression in specific CTD-ILD patients such as SjD-ILD, MCTD-ILD or SLE-ILD.

Indirect evidence

Limited indirect evidence comes from studies focused on treatment with immunosuppressants for ILD including some patients with SjD-, MCTD- or SLE-ILD without subgroup analyses on these patient subgroups. We, therefore, decided to use this evidence from studies with pooled CTD-ILD patients including specific CTDs mentioned above as indirect evidence. Patients with other CTD-ILDs were included in RCTs such as RECITAL [258] and EVER-ILD [300]. In RECITAL, including 16 MCTD out of 101 CTD-ILD patients, FVC increased with both cyclophosphamide and rituximab treatment at 24 weeks, in addition to clinically important improvements in HRQoL. The EVER-ILD trial included 43 CTD-ILD patients, with rituximab plus MMF showing superiority over MMF alone, with an FVC improvement of +1.53% *versus* −2.04%. Retrospective non-controlled studies reported varying results for FVC % for different agents [326–328]. Regarding adverse events, in the RECITAL study, gastrointestinal disorders, general disorders, administration site reactions and nervous system disorders were more common with cyclophosphamide than rituximab. Infection rates were similar between groups, with no subgroup analysis conducted [258]. In the EVER-ILD trial, infections were numerically higher in the MMF plus rituximab group compared to the MMF plus placebo group, but no disease-specific analysis was performed [300]. Similar rates of adverse events occurred between azathioprine and MMF in CTD-ILD patients, and there was at least one documented infection within 1 year of treatment in 27% of patients treated with rituximab [328,329].

Justification of recommendation

We suggest using immunosuppressive therapy for other CTD-ILD based on indirect evidence indicating potential improvement or stabilisation in FVC % and D_{LCO} %, with an acceptable safety profile. This recommendation is conditional due to the very low certainty of evidence and the lack of specific clinical trials for patients with SjD-, MCTD- or SLE-associated ILD. The available data comes from studies that included broader populations, without focusing on these specific CTD-ILD subgroups.

PICO question 19

Should nintedanib *versus* control be used for patients with SSc-ILD?

Recommendation

We suggest using nintedanib in patients with SSc-ILD (conditional recommendation, moderate certainty of evidence).

Summary of evidence

We included one study (SENSCIS) [246] comparing the effects of 150 mg of nintedanib (n = 264), taken orally twice daily, with placebo (n = 275) in patients with SSc-ILD over a 52-week period. Patients taking nintedanib experienced a mean absolute difference of 41 mL (95% CI 2.9 to 79) in FVC compared with placebo, with no difference in D_{LCO} between the groups. No significant differences in in mortality, mRSS, SGRQ-measured symptom burden, FACIT-dyspnoea scale, HRQoL measured by HAQ-DI or digital ulcer net burden were observed between nintedanib and placebo. The nintedanib group had a higher incidence of adverse events compared to the placebo group, with an OR 2.46 (95% CI 0.86 to 7.08) and 24 more events per 1000 patients, though this difference was not statistically significant. Diarrhoea was frequent and higher in the nintedanib than the placebo group (75.7% *versus* 31.6%). Drug discontinuation due to side-effects was higher in the nintedanib than in the placebo group (16.0% *versus* 8.7%). There was serious imprecision in the critical outcomes and the overall certainty of evidence was moderate.

Indirect evidence

A *post hoc* analysis of the SENSCIS trial [208] revealed that patients experiencing FVC improvements or deteriorations (FVC >10% or <10% over 52 weeks) had corresponding changes in symptom burden assessed by SGRQ. *Post hoc* analyses indicated treatment efficacy across all subgroups [245,330]. Long-term data from the SENSCIS-ON [239,331], the open-label extension study, suggested sustained effects of nintedanib on lung function over 3 years, although the discontinuation due to adverse events was higher with nintedanib compared with placebo (7.3%). Subgroup analyses indicated differences in adverse events, with hepatic events more common in Asian women and severe adverse events more frequent in men [332,333].

Justification of recommendation

We suggest using nintedanib in patients with SSc-ILD as it reduces FVC decline in patients with SSc-ILD with >10% fibrosis extent. Our recommendation is conditional based on moderate certainty of evidence. This was mainly due to imprecision, only effecting FVC, but not other important outcomes such as extrapulmonary organ involvement, other pulmonary outcomes, quality of life and symptom burden.

PICO question 20

Should nintedanib *versus* control be used for patients with any CTD-ILD?

Recommendation

We suggest using nintedanib in any CTD-ILD patients with progressive pulmonary fibrosis (conditional recommendation, low certainty of evidence).

Summary of evidence

We identified one RCT (INBUILD) [243], with different subgroups of progressive ILD including 89 RA-ILD, 39 SSc-ILD, 19 MCTD-ILD, and 23 other autoimmune disease-related ILDs, of which seven had SjD, comparing nintedanib with placebo. Nintedanib at a dose of 150 mg twice daily slowed the decline of FVC compared to placebo over a mean follow-up period of 52 weeks, with a mean difference of 107 mL (95% CI 104.66 to 109.34) in the total study population. Mortality rates between the two groups showed no significant difference in the overall group. The K-BILD score did not differ between the groups. Adverse events were more frequent with nintedanib, with 317 out of 332 (95.5%) patients in the nintedanib and 296 out of 331 (89.4%) patients in the placebo group experiencing adverse events (OR 2.50, 95% CI 1.34 to 4.67). There was serious

indirectness and serious imprecision in the critical outcomes and the overall certainty of evidence was low.

Indirect evidence

In the subgroup of patients with CTD-ILDs included in the above-mentioned trial assessing nintedanib in progressive ILD patients, there were no significant differences in mortality (HR 0.80, 95% CI 0.32 to 1.98; p = 0.62) [267]. In a retrospective study reported by Liang *et al.* [285], 36 patients on combined immunosuppression and nintedanib experienced better survival and reduced disease progression compared to the 115 on immunosuppressive agents alone. The incidence of diarrhoea in the nintedanib group was 44.4%. Adverse events such as nausea, vomiting, liver enzyme elevations, dose reductions and treatment interruptions were more common among female patients with CTD-ILDs compared to male patients [332].

Justification of recommendation

We suggest using nintedanib for patients with any CTD-ILD, including RA-ILD, who experience progressive pulmonary fibrosis despite adequate treatment, as it has been shown to slow FVC decline. This recommendation is conditional because of the low certainty of evidence (based on imprecision and indirectness), because data are derived from a subgroup of progressive CTD-ILD patients, and because data on important outcomes such as extrapulmonary organ involvement and other pulmonary effects are lacking.

PICO question 21

Should pirfenidone *versus* control be used for patients with RA-ILD?

Recommendation

We suggest using pirfenidone in patients with RA-ILD and a UIP pattern (conditional recommendation, very low certainty of evidence).

Summary of evidence

There is one multicentre phase 2 RCT (TRAIL-1) [264] that evaluated efficacy of 2403 mg oral pirfenidone in RA-ILD compared to placebo (n = 123). The trial was underpowered and terminated early based on futility. Mortality rates did not differ between groups (OR 0.62, 95% CI 0.10 to 3.87). The mean difference in the annual change in FVC between pirfenidone and placebo was 80 mL (95% CI 22 to 138), with the most pronounced efficacy in patients with a UIP pattern. There were no differences in hospitalisation rates and symptom burden. Adverse events were more common in the pirfenidone group (98.4%) compared to placebo (93.3%). There was serious risk of bias and very serious imprecision in the critical outcomes, and the overall certainty of evidence was very low.

Indirect evidence

The RELIEF study [334], an RCT examining the efficacy of pirfenidone in patients with progressive fibrotic ILDs other than idiopathic pulmonary fibrosis (IPF), included 17 patients (46%) with RA. Despite its premature termination due to slow recruitment, pirfenidone significantly slowed FVC decline in the overall patient group. When stratified by diagnostic groups, including CTD-ILD, the significance persisted. Adverse events were similar between the pirfenidone and placebo groups.

Justification of recommendation

We suggest using pirfenidone in patients with RA-ILD as it reduces FVC decline, especially in patients with a UIP pattern. Our recommendation is conditional, due to very low certainty of evidence mainly due to risk of bias, and imprecision, no effect on symptom burden and the lack of information on other important outcomes such as extrapulmonary organ involvement and quality of life.

PICO question 22

Should pirfenidone *versus* control be used for patients with any CTD-ILD other than RA-ILD?

Recommendation

We could not make recommendations for the use of pirfenidone in patients with any CTD-ILD other than in RA-ILD due to a paucity of evidence.

Summary of evidence

No studies were identified.

Indirect evidence

The RELIEF study [334], an RCT examining the efficacy of pirfenidone in patients with progressive fibrotic ILDs other than IPF, included 17 patients (46%) with RA, eight (22%) with SSc, five (14%) with SjD and IIM, three (8%) with MCTD, and four (11%) with an overlap syndrome. Pirfenidone significantly slowed FVC decline in the overall patient group. When stratified by diagnostic groups, including CTD-ILD, the significance persisted. Adverse events were evenly spread between the pirfenidone and placebo groups.

PICO question 23

Should combination therapy with nintedanib and MMF *versus* control be used for patients with SSc-ILD?

Recommendation

We suggest using combination therapy with nintedanib and MMF in patients with SSc-ILD (conditional recommendation, low certainty of evidence).

Remark

In the SENSCIS study patients were on stable dose background MMF. The current evidence is therefore derived from adding nintedanib on top of stable MMF treatment.

Summary of evidence

We identified one RCT assessing combination therapy (SENSCIS) [335]. In the trial, 139 of 288 (48%) were treated with nintedanib and MMF, whereas 52% were only using nintedanib and 140 (49%) only MMF. Figure 2 shows the comparison of nintedanib and MMF with placebo, and MMF was associated with an MD in FVC of 26.3 mL (95% CI 27.9 to 80.5) at 52 weeks. Mortality rates did not differ in the nintedanib plus MMF group compared to the placebo plus MMF. Extrapulmonary manifestations, assessed by the mRSS, and symptom burden, measured by SGRQ, showed no significant difference between the two groups. Adverse events were more frequent in the nintedanib plus baseline MMF group compared to the placebo plus baseline MMF group, but not the nintedanib alone group. There was very serious imprecision in the critical outcomes and the overall certainty of evidence was low.

Indirect evidence

In the INBUILD trial [267] sub-analyses, which included 39 SSc-ILD patients, the effect of nintedanib on FVC decline was consistent across subgroups with and without disease modifying anti-rheumatic drugs and/or glucocorticoids. Observational studies in SSc-ILD explored combinations such as rituximab with glucocorticoids or other disease modifying anti-rheumatic drugs but direct efficacy comparisons were lacking [251,292,336].

Justification of recommendation

We suggest using combination therapy with nintedanib and MMF in patients with SSc-ILD as it reduces FVC decline in a representative SSc-ILD population without increasing harm compared to monotherapy. However, our recommendation is conditional, due to the low certainty of evidence. This was due to indirectness, imprecision, and no effect on other important outcomes such as extrapulmonary organ involvement, other pulmonary outcomes, quality of life and symptom burden.

PICO question 24

Should combination therapy *versus* control be used for patients with IIM-ILD?

Recommendation

We suggest using combination therapy with immunosuppressants including glucocorticoids in patients with IIM-ILD (conditional recommendation, very low certainty of evidence).

Remark

We suggest considering timely intervention with combination therapy for patients with IIM-ILD, with the intensity and combination of immunosuppressive agents depending on the risk of progression and/or development of severe ILD. Combination therapy may also be important to avoid long-term glucocorticoid treatment.

Summary of evidence

Three retrospective studies were identified [302–304]. The first study added IVIG to immunosuppressive therapy for newly diagnosed MDA-5-positive IIM-ILD patients, comparing it to immunosuppressants alone [302]. The second study examined tacrolimus added to conventional therapy in dermatomyositis and polymyositis patients *versus* conventional therapy alone [304]. The third compared a combination of calcineurin inhibitors and high-dose glucocorticoids with high-dose glucocorticoids alone in dermatomyositis and polymyositis patients [303]. Mortality rates differed significantly between treatment groups (4.2–23% with IVIG or tacrolimus added to immunosuppressive treatment, compared to 20–53% with immunosuppressive treatment alone; $p = 0.008–0.033$). FVC % predicted improved in both groups. D_{LCO} % predicted showed minor variations. Extrapulmonary improvements were observed in manual muscle testing and creatine kinase levels, without direct comparisons. Improvements in imaging findings were noted in both treatment groups, without direct comparisons. There was serious risk of bias and very serious imprecision in the critical outcomes and the overall certainty of evidence was very low.

Indirect evidence

Studies of combination therapies in IIM-ILD, including tacrolimus or cyclosporin A with glucocorticoids, have shown benefits such as improved survival, lung function (FVC and D_{LCO}), and extrapulmonary involvement [274]. Combination treatment of glucocorticoids with immunosuppressants has also led to improved lung function outcomes [278,279,306,307]. Additionally, tofacitinib combined with glucocorticoids demonstrated improved survival, FVC, and radiographic appearance of ILD on HRCT [272]. Studies have also indicated that adding tofacitinib to other immunosuppressive therapies and glucocorticoids can improve survival in MDA-5-positive IIM-ILD patients. In the EVER-ILD trial, ILD patients received rituximab or placebo in addition to MMF, with the combination found to be superior in terms of the change in FVC % predicted [300]. However, no subgroup analyses specific to CTD-ILD patients were reported.

Justification of recommendation

We suggest using combination therapy with immunosuppressants – such as calcineurin inhibitors, high-dose glucocorticoids, and/or IVIG along with standard immunosuppressive treatment – for patients with IIM-ILD, as it has been shown to improve FVC and D_{LCO}, and may reduce mortality, pulmonary opacities on HRCT, and extrapulmonary organ involvement without increasing harm. This recommendation is conditional due to the very low certainty of evidence based on risk of bias, and imprecision, the limited number of combination therapies studied, and the lack of reporting on important outcomes such as quality of life and symptom burden.

PICO question 25

Should combination therapy *versus* control be used for any patient with CTD-ILD?

Recommendation

We suggest treating patients with any CTD-ILD with a combination of immunosuppressants or, in the presence of progressive pulmonary fibrosis, with a combination of an immunosuppressant and nintedanib (conditional recommendation, very low certainty of evidence; no studies included).

Summary of evidence

We did not identify any study. The recommendation is based on indirect evidence outlined in the indirect evidence below.

Indirect evidence

In the EVER-ILD trial [300], which also included patients with CTD-ILD, ILD patients received rituximab or placebo in addition to MMF, with the combination proving superior in terms of change in FVC % predicted. No subgroup analyses of CTD-ILD patients were reported. Similarly, in the INBUILD trial [267], there was no heterogeneity in the effect of nintedanib *versus* placebo on the annual rate of decline in FVC across subgroups according to baseline use of disease modifying anti-rheumatic drugs, glucocorticoids and nintedanib. Observational studies in SSc-ILD have explored combination therapies such as rituximab, tocilizumab, and other biologic or conventional disease modifying anti-rheumatic drugs [251,292,336]. In the INBUILD trial [267], adverse profiles were comparable among autoimmune ILD patients. In the EVER-ILD trial [300], ILD patients receiving rituximab in combination with MMF showed a higher incidence of infections compared to MMF alone. No subgroup analyses of CTD-ILD patients were reported. In RA-ILD, retrospective analyses suggested that adding nintedanib or pirfenidone to immunosuppressive treatment was well-tolerated [272].

Justification of recommendation

We suggest treating patients with any CTD-ILD who are at high risk of progression with a combination of immunosuppressants or, in cases of progressive pulmonary fibrosis, with a combination of an immunosuppressant and nintedanib, as data indicate efficacy in stabilising FVC. However, this recommendation is conditional due to the very low certainty of evidence, which is based on indirect data, the limited number of combination therapies studied, and evidence of increased adverse events with rituximab and MMF combination therapy. Additionally, important outcomes such as quality of life and symptom burden were not adequately assessed.

Narrative question 28

Can key factors be used for the choice of treatment for CTD-ILD?

Recommendation

We suggest using the inclusion criteria of RCTs to guide treatment decisions for CTD-ILD (conditional recommendation, very low certainty of evidence).

Summary of evidence

We did not identify any study. The recommendation is based on indirect evidence outlined below.

Indirect evidence

The task force found no direct evidence. We therefore based our recommendation on indirect evidence. Using the inclusion criteria of RCTs for interventions in clinical practice may help to identify eligible patients for a specific therapeutic option. However, it should be realised that trials in this fields are limited, and trial criteria often do not capture the full spectrum of disease presentations encountered in real-world settings, potentially excluding patients who could benefit. For instance, the efficacy of tocilizumab was assessed in a phase 2 and a phase 3 trial including inflammatory, diffuse cutaneous, early, skin progressive SSc-ILD patients. The efficacy of tocilizumab was then examined in various studies applying the inclusion criteria as outlined in the indirect evidence of PICO question 13. While studies mirroring the FocuSSced trial criteria showed similar FVC behaviour as the placebo group of the trial, another study not using the inclusion criteria failed to demonstrate treatment efficacy in SSc patients [114,232,248,292]. Another example is the INBUILD trial. All patients that were included had progressive pulmonary fibrosis as defined as: relative decline in FVC % ≥10%; relative decline in FVC % ≥5% to <10% and worsened respiratory symptoms; relative decline in FVC % ≥5% to <10% and increased extent of fibrosis on HRCT; worsened respiratory symptoms and increased extent of fibrosis on HRCT [267]. The study showed that nintedanib had a significant effect on slowing FVC decline in this study population.

Justification of the recommendation

We suggest using the inclusion criteria of RCTs to guide treatment decisions in CTD-ILD where available as the demonstrated efficacy has been shown in selected CTD-ILD populations and may not be generalisable to others. Our recommendation is conditional because the evidence is of very low certainty, based on indirect data, and key factors influencing treatment choices have not been directly assessed.

Treatment algorithm

The task force proposes some overarching treatment principles. Firstly, highly specialised and off-label therapy, *i.e.* non-licensed therapy, should be prescribed in expert centres or centres with ILD and CTD expertise. Next, multidisciplinary discussions that include pulmonologists and rheumatologists are advised. Lastly, reimbursement, availability and labelling in the respective countries, and patient preferences need to be considered when choosing treatment(s). The treatment algorithms are entirely based on the identified therapeutic options from the PICO and narrative questions of this guideline and are presented as alternatives without hierarchy, as we did not include a narrative question on hierarchy and no head-to-head clinical trials were identified. RCTs should guide therapy decisions where available, and the inclusion criteria of the trials may be applied to choose the right therapeutic agent for the individual patient where available until clear key factors are identified and more data are available (narrative question 28). In addition, choice of therapy should consider extrapulmonary organ manifestations, potential harm such as side-effects and risk of progressive ILD using risk factors for poor outcome (narrative questions 8–11 and PICO questions 12–25). Early and/or aggressive treatment is proposed for patients at risk of progressive or at risk of developing severe ILD, and for patients with multiple risk factors or specific indicators, such as anti-MDA-5 autoantibodies (narrative questions 8–11). If other treatment guidelines are available for extrapulmonary organ involvement, these should be considered, including the EULAR treatment recommendations for RA [337] and SSc [338]. For patients with RA-ILD, the presence of active or well-controlled arthritis concurrent with ILD will define which treatments could be considered. Case by case discussions are advised for starting drugs such as TNFi, which may aggravate existing ILD, until more comprehensive data become available for potential beneficial effects and harms. There is increasing evidence that methotrexate, which in rare cases may induce acute pneumonitis, is beneficial in RA-ILD patients [137,323].

EXECUTIVE SUMMARY OF THE GUIDELINE

Our guideline provides comprehensive support for clinicians and patients, encompassing screening, diagnosis, monitoring and treatment strategies for people with CTD-ILD. Many of the pre-defined management areas are addressed specifically for the underlying rheumatic disease, which is of importance due to the inherent differences across the diseases.

We recommend screening all patients with SSc, MCTD and IIM patients with risk factors using HRCT at time of diagnosis. We suggest that most patients with IIM without risk factors except for inclusion body myositis as well as patients with RA and SjD who have risk factors for ILD should be screened for ILD using HRCT. We suggest that lung biopsy does not play a role in the diagnosis of CTD-ILD but might be considered in an multidisciplinary team discussion if alternative diagnoses are considered [339]. In the case of possible alternative diagnoses or co-existing conditions, BAL could be considered together with other assessments to rule out differential diagnoses, but does not routinely play a role in the diagnosis of ILD in CTDs. We suggest that, at the time of ILD diagnosis, all patients should be assessed for disease severity and risk of progression by performing a risk factor assessment, as well as PFTs, HRCT, 6MWT and PROMs.

For monitoring all CTD-ILD patients, we suggest conducting a comprehensive evaluation during each visit to identify

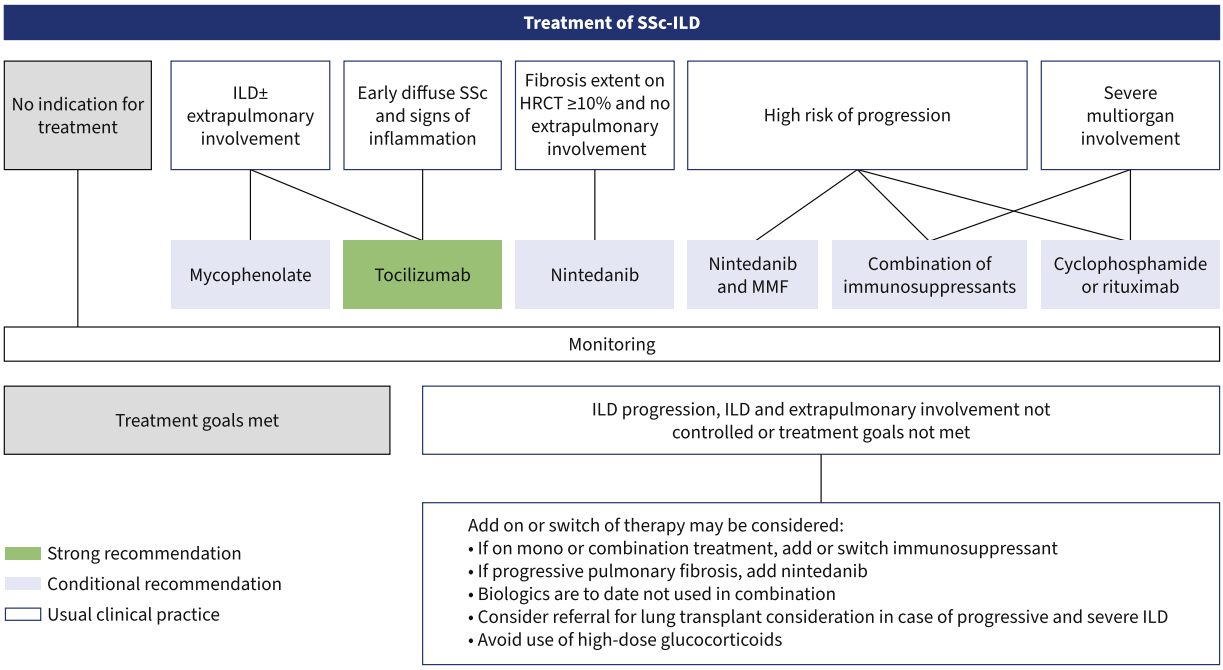

Figure 4a. Treatment algorithms for patients with systemic sclerosis (SSc)-associated interstitial lung disease (ILD). HRCT: high resolution computed tomography; MMF: mycophenolate mofetil.

individuals at high or low risk for poor prognosis, ILD progression, and disease severity. Clinical risk factors can be used to identify patients at high or low risk of progression. High risk patients are suggested to be followed with lung function tests every 3–6 months early in the disease course and every 6–12 months thereafter. A control HRCT is suggested to be conducted routinely after 12 months, followed by annual HRCT if clinically indicated. The 6MWT in patients without physical limitations and PROMs are suggested to be conducted every 6–12 months in usual clinical practice. PROMs can provide valuable insights into the patient's perspective, capturing respiratory symptoms in a validated and standardised way, and assessing the impact of the disease on daily life and patient well-being, which can enhance the overall assessment of disease severity and treatment effectiveness. Patients at lower risk are suggested to be followed with the same assessments but over longer time intervals.

The treatment recommendations are comprehensive and summarised per disease, including key factors for choice of treatment in the provided treatment algorithms. In summary, therapy choice should consider patient-specific risk factors, extrapulmonary organ manifestations, potential side-effects, and the risk of progressive or severe ILD. Early and/or aggressive treatment is recommended for patients at risk of progressive

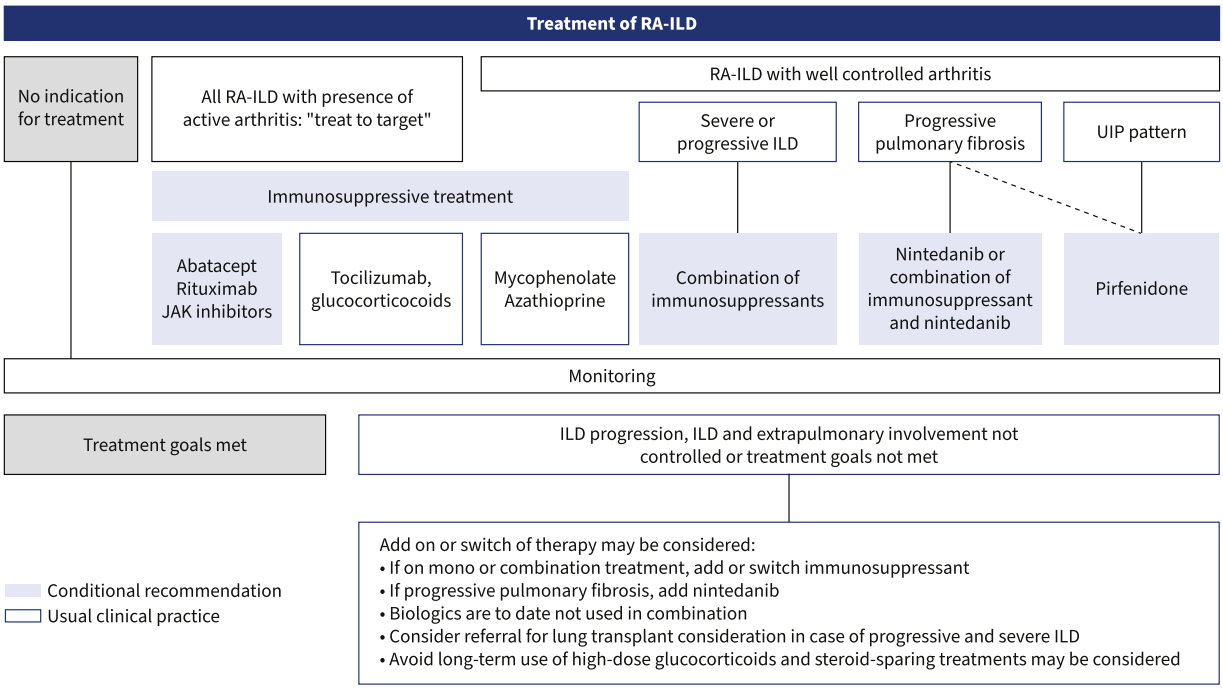

Figure 4b. Treatment algorithms for patients with rheumatoid arthritis (RA)-associated interstitial lung disease (ILD). UIP: usual interstitial pneumonia; JAK: Janus kinase.

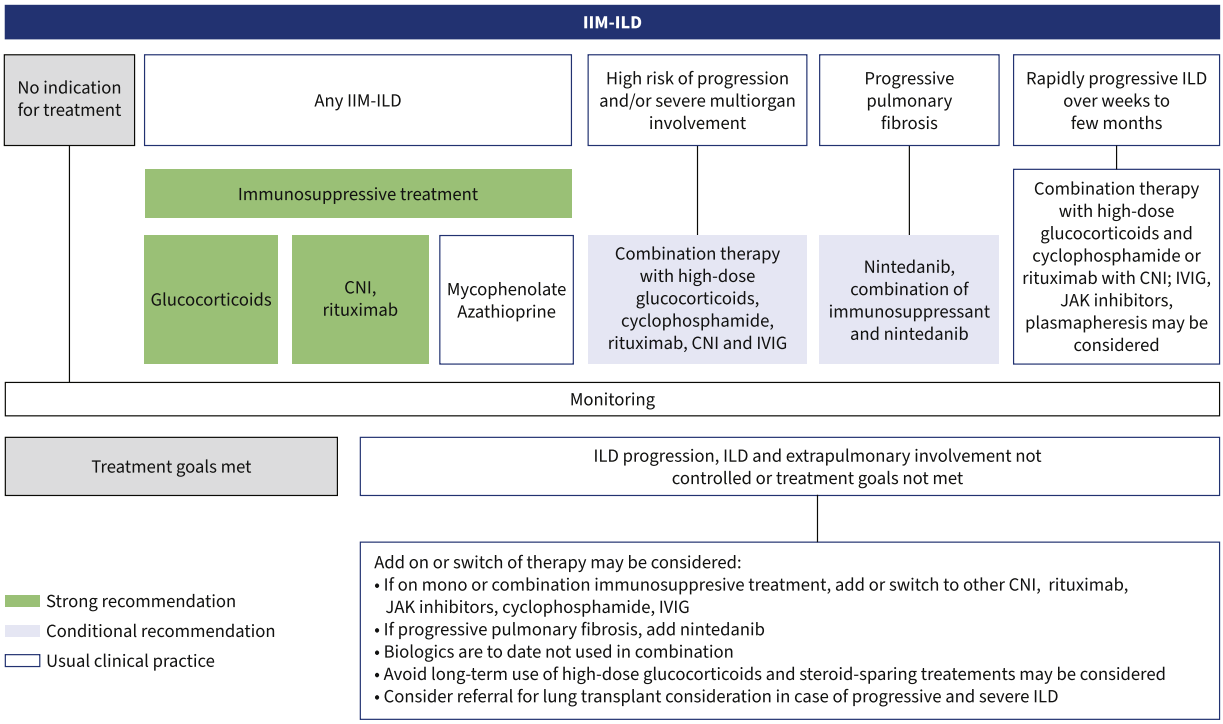

Figure 4c. Treatment algorithms for patients with interstitial lung disease (ILD) associated with idiopathic inflammatory myopathies (IIM). CNI: calcineurin inhibitor; IVIG: intravenous immunoglobulins; JAK: Janus kinase.

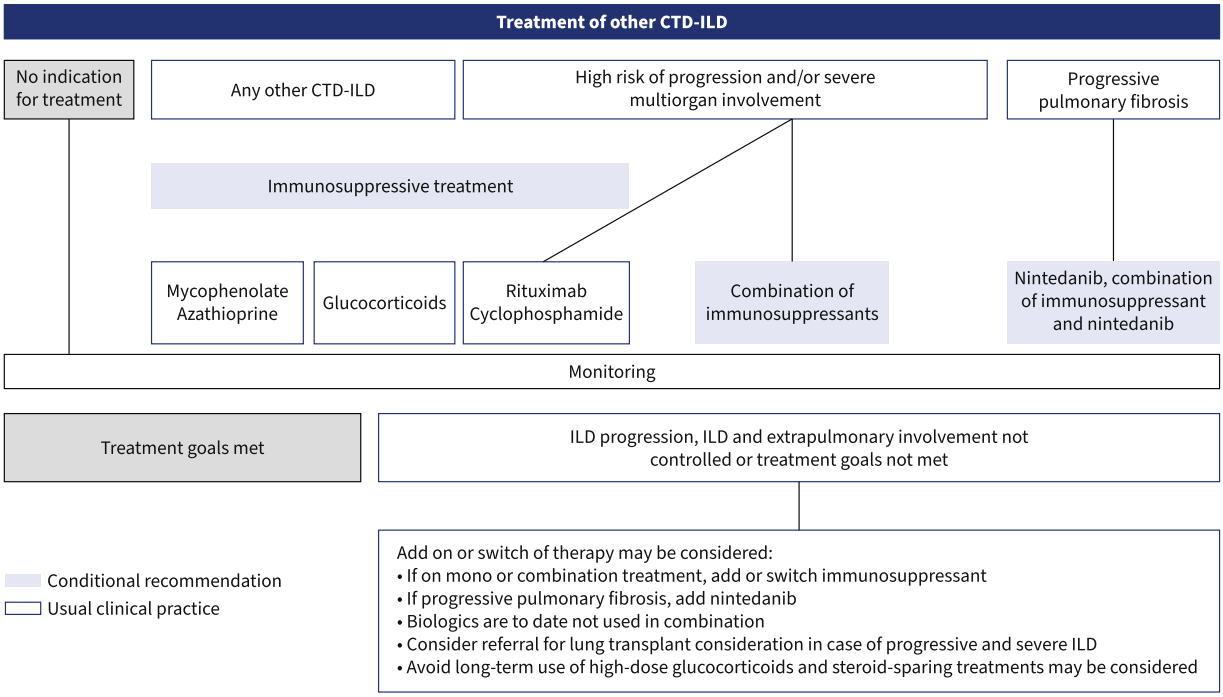

Figure 4d. Treatment algorithms for other connective tissue disease (CTD)-associated interstitial lung disease (ILD) patients, such as Sjögren disease-, mixed connective tissue disease- or systemic lupus erythematosus-associated ILD.

or severe ILD, especially those with multiple risk factors or specific indicators like anti-MDA-5 autoantibodies. Specifically, for SSc-ILD, it is suggested to use MMF, rituximab and cyclophosphamide. For early diffuse cutaneous SSc characterised by increased inflammatory markers or recent skin fibrosis progression, tocilizumab is recommended. Nintedanib is suggested for SSc-ILD patients, as well as the combination of nintedanib and MMF (figure 4a). Regarding RA-ILD, immunosuppressive treatment, and the use of pirfenidone for patients displaying a UIP pattern, are suggested (figure 4b). In IIM-ILD, immunosuppressive treatment is recommended. Moreover, the use of combination therapy involving immunosuppressants and glucocorticoids is suggested (figure 4c). In other CTD-ILDs, including SjD-, MCTD- and SLE-ILD, immunosuppressive treatment is suggested. Nintedanib and combination therapy is suggested for any CTD-ILD patients who exhibit progressive pulmonary fibrosis (figure 4d). In addition to pharmacological therapy, we encourage adhering to non-pharmacological treatment and

existing specific rheumatic disease recommendations in addition to our ILD-specific guideline to guarantee an optimised and holistic disease management [340,341].

Our guideline has some limitations. Our guideline predominantly builds on evidence of low and very low certainty. This is a common challenge for rare diseases, attributable to limited patient populations and a scarcity of RCTs with adequate numbers of participants needed to achieve a high level of evidence. This led to most recommendations being conditional. Consequently, we deem our research agenda highly significant and advocate undertaking studies to address these gaps. Using the GRADE methodology agreed on by both societies did not allow us to record level of agreement and this is the reason why this is not reported. Lastly, our guideline is only developed for adult patients, and some aspects may be different in childhood populations.

Competing interests

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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