Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-320-z Nintedanib

Stand: Februar 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Nintedanib
[zur Behandlung interstitieller Lungenerkrankung mit systemischer Sklerose (SSc-ILD) bei Kindern und Jugendlichen]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht "II. Zugelassene Arzneimittel im Anwendungsgebiet"*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Langzeit-Sauerstofftherapie • Lungentransplantation • Pulmonale Rehabilitation • Physikalische Therapie (i.S. der Heilmittel-RL)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Nintedanib *(D-546 – Beschluss vom 04. Februar 2021)*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nintedanib L01XE31 Ofev®	Anwendungsgebiet laut Positive Opinion vom 13.12.2024: Ofev is indicated in adults, adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).
Methylprednisolon H02AB04 Methylprednisolon Jenapharm®	Bronchial- und Lungenkrankheiten […] – Interstitielle Lungenerkrankungen, wie akute Alveolitis, Lungenfibrose, zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte)
Prednisolon H02AB06 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […]
Prednison H02AB07 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […]

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-320-z (Nintedanib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	29. Januar 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DLCO	Diffusing capacity of the lung for carbon monoxide
ECRI	ECRI Guidelines Trust
FACIT	Functional Assessment of Chronic Illness Therapy
FVC	Forced Vital Capacity
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAQ-DI	Health Assessment Questionnaire–Disability Index
HR	Hazard Ratio
HRCT	High-resolution chest computed tomography
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MCID	Minimal clinically important difference
MMF	Mycophenolate
mRSS	modified Rodnan Skin Score
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PF-ILD	Progressive fibrosing Interstitial Lung Disease
QILD	Quantitative ILD
QLF	Quantitative lung fibrosis
RR	Relatives Risiko
SGRQ	St. George’s Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SoR	Strength of Recommendation
SSc-ILD	Systemic Sclerosis-associated Interstitial Lung Disease
TDI	Transition Dyspnea Index
TRIP	Turn Research into Practice Database
UIP	Usual interstitial pneumonia
WHO	World Health Organization

1 Indikation

Treatment for adults, adolescents and children aged 6 years and older for systemic sclerosis associated interstitial lung disease (SSc ILD).

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *interstitielle Lungenerkrankung und systemischer Sklerose* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 02.01.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1996 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 2 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine systematischen Reviews identifiziert.

3.3 Leitlinien

Raghu G et al., 2024 [2].

American Thoracic Society

Treatment of Systemic Sclerosis-associated Interstitial Lung Disease: Evidence-based Recommendations. An Official American Thoracic Society Clinical Practice Guideline

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu (Suchzeitraum und -Trefferzahl nicht genannt);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft teilweise zu (externes Begutachtungsverfahren nicht beschrieben);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- The Ovid platform was used to search MEDLINE, EMBASE, Cochrane Registry of Controlled Trials, Health Technology Assessment, and the Database of Abstracts of Reviews of Affects.

LoE/GoR

- **quality of evidence** was determined using the GRADE approach and categorized as high, moderate, low, or very low.
- **Recommendations** were either “strong” or “conditional” (or “weak”) in favor of or against each therapy.

Stakeholder	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but some would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Table 1: Implications of the Guideline Recommendations for Patients with Systemic Sclerosis associated Interstitial Lung

Empfehlungen

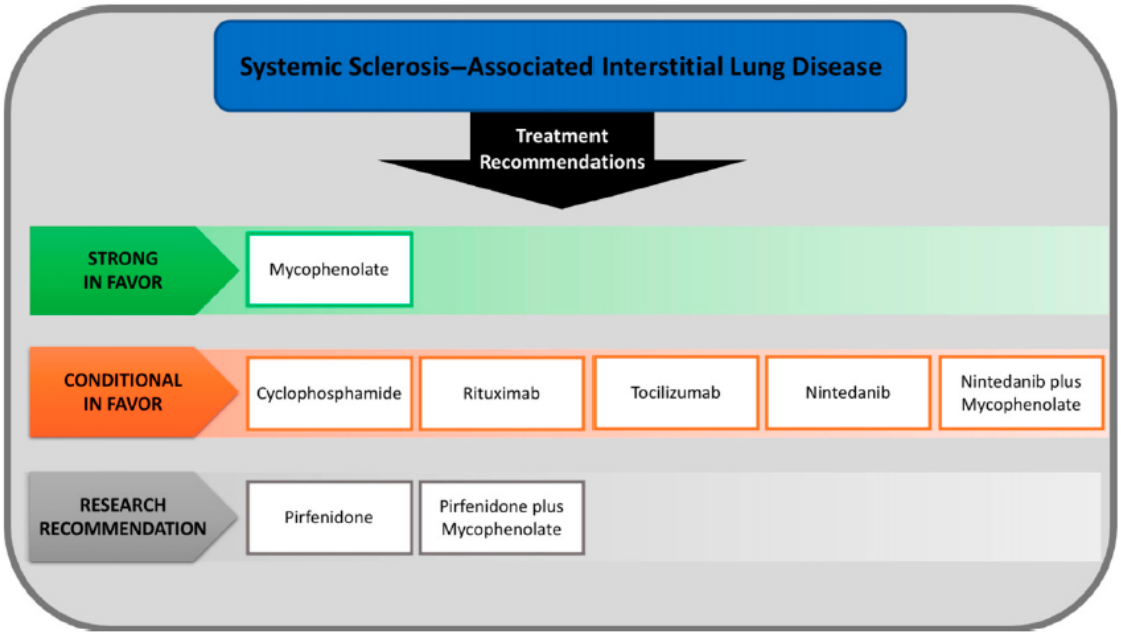

Figure 1. Summary of treatment recommendations for patients with systemic sclerosis–associated interstitial lung disease (SSc-ILD). The SSc-ILD Guideline Committee:

1) Recommends the use of *mycophenolate* to treat patients with SSc-ILD *(18 votes: 14 strong recommendation for use, 4 conditional recommendations for use).*
2) Suggests the use of *cyclophosphamide* to treat patients with SSc-ILD *(17 votes: 5 strong recommendation for use, 12 conditional recommendations for use).*
3) Suggests the use of *rituximab* to treat patients with SSc-ILD *(18 votes: 1 strong recommendation for use, 16 conditional recommendation for use, 1 abstention due to insufficient expertise).*
4) Suggests the use of *tocilizumab* to treat patients with SSc-ILD *(16 votes: 16 conditional recommendation for use).*
5) Suggests the use of *nintedanib* to treat patients with SSc-ILD *(14 votes: 1 strong recommendation for use, 11 conditional recommendation for use, 1 conditional recommendation against use, 1 abstention due to insufficient expertise).*
6) Suggests the use of *nintedanib* plus mycophenolate to treat patients with SSc-ILD *(14 votes: 1 strong recommendation for use, 11 conditional recommendation for use, 2 abstentions due to insufficient expertise).*
7) Recommends further research into the efficacy, effectiveness, and safety of *pirfenidone* to treat patients with SSc-ILD *(13 votes: 2 conditional recommendation against use, 11 abstentions due to insufficient evidence).*
8) Recommends further research into the efficacy, effectiveness, and safety of *pirfenidone* plus mycophenolate to treat patients with SSc-ILD *(13 votes: 1 conditional recommendation against use, 12 abstentions due to insufficient evidence).*

The above recommendations were not assessed as a stepwise algorithm. Clinicians are encouraged to use these recommendations in conjunction with shared decision-making with patients, incorporating side effects and personal values and preferences before administration.

Hintergrund:

- **Question 1: Should patients with SSc- ILD be treated with cyclophosphamide?**

Summary of evidence:

A systematic review of the evidence identified five studies (see Table E1 in the online supplement). Two RCTs compared cyclophosphamide to placebo. SLS I (Scleroderma Lung Study I) was a 24-month, multicenter U.S.-based, NIH-funded RCT that randomized patients to 12months of cyclophosphamide or 12months of placebo followed by 12months off therapy. SLS I included participants with SSc and with active alveolitis on BAL or ground-glass opacity on high-resolution CT (HRCT) of the chest and at least moderate dyspnea (4). Hoyles and colleagues reported on a multicenter U.K.-based, charitable donation–funded RCT including participants with SSc and evidence of pulmonary fibrosis on HRCT or lung biopsy that compared placebo to a regimen of intravenous cyclophosphamide monthly for 6 months plus prednisolone 20mg every other day followed by azathioprine (24). One RCT and two case–control studies compared the use of cyclophosphamide to mycophenolate. SLS II was a multicenter, U.S.-based, NIH-funded, double-blind RCT that compared oral cyclophosphamide for 12 months followed by placebo for 12 months to oral mycophenolate for 24months (5). Shenoy and colleagues (25) and Panopoulos and colleagues (26) were both retrospective, single-center, unfunded case–control studies that identified patients with SSc-ILD who had been treated with intravenous or oral cyclophosphamide and compared outcomes with patients who were treated with oral mycophenolate for 12 or 24months. There was not enough evidence to be able to separate cyclophosphamide therapy by route of administration. DISEASE PROGRESSION. When compared with placebo, the mean change in FVC % predicted at 12months was 2.8%, favoring cyclophosphamide. Treatment with cyclophosphamide was associated with an improvement in FVC % predicted at 12months in a greater proportion of participants compared with placebo (49.3% vs. 26.4%, respectively). At 24months, the mean values of FVC % predicted were similar between treatment and placebo groups. There was no difference in DLCO % predicted between groups at 12 or 24months.When cyclophosphamide was compared with mycophenolate, there was a difference in DLCO % predicted favoring mycophenolate at 6 months and 18 months, but not at 12 months or 24months.When cyclophosphamide was compared with mycophenolate, both groups showed an improvement in FVC % predicted, but there was no difference between the two groups at any time point. The change from baseline at 12months for them RSS was 3.06 better in the subset of patients with diffuse SSc. MORTALITY. When comparing placebo and cyclophosphamide, there was no difference in mortality at 12 or 24months. When comparing cyclophosphamide to mycophenolate, there was no difference in mortality between groups at 24months. QUALITY OF LIFE. When compared with placebo, there was a significant improvement in the cyclophosphamide arm for breathlessness and disability according to the HAQ-DI. When comparing cyclophosphamide tomycophenolate, although both arms showed significant improvement in quality of life (QoL) outcomes such as breathlessness, cough, and disability, there was no difference between groups. ADVERSE EVENTS. When compared with placebo, there was a 15-fold increased risk of hematologic adverse events using cyclophosphamide at 12months, including leukopenia (requiring discontinuation in seven cyclophosphamide cases) and thrombocytopenia. There was also a fourfold increased risk of infections using cyclophosphamide at 12months. At 24months, there was an increased risk of constitutional symptoms using cyclophosphamide. There was no increased incidence of hematuria or hemorrhagic cystitis using cyclophosphamide compared with placebo (27). When compared with mycophenolate, participants were 1.7 times more likely to prematurely discontinue cyclophosphamide therapy. There was a six-fold increased risk of leukopenia using cyclophosphamide compared with mycophenolate, but there was no difference in any other reported adverse events.

Quality of evidence:

The quality of evidence was rated as low for these outcomes, which means there was low confidence in the estimated effects. Therefore, the data should be interpreted with caution. Quality of evidence was reduced in cyclophosphamide compared with placebo because few trials studied this comparison, leading to imprecision, and the intervention in Hoyles and colleagues included azathioprine and prednisolone as well as cyclophosphamide (24). The quality of evidence was low for the cyclophosphamide versus mycophenolate comparison because of imprecision, study design (retrospective case–control studies), and indirectness of the comparator (multiple formulations of mycophenolate).

Recommendation 1:

We suggest using cyclophosphamide to treat patients with SSc-ILD (conditional recommendation, low quality evidence).

The committee vote was as follows: strongly in favor to use cyclophosphamide in people with SSc-ILD: 5 of 17 (29%); conditional recommendation to use cyclophosphamide in people with SSc-ILD: 12 of 17 (71%); conditional recommendation to not consider cyclophosphamide: 0 of 17 (0%); strong recommendation to not consider cyclophosphamide: 0 of 17 (0%). No guideline participants (0%) abstained from this vote.

- **Question 2: Should patients with SSc-ILD be treated with mycophenolate?**

Summary of evidence:

A systematic review of the evidence identified seven total studies (5, 25, 26, 31–34) (Table E2). Two were RCTs (5, 32): three were post hoc analyses of RCTs (31, 33, 34), and two were observational studies (25, 26). Two studies compared mycophenolate to placebo (32, 34), and five compared mycophenolate to

cyclophosphamide (5, 25, 26, 31, 33). The predominance of data comparing mycophenolate to placebo was from a post hoc study that compared those who received mycophenolate in SLS II with those patients who received placebo in SLS I (34). The SLS II trial provided the majority of evidence for the comparison between mycophenolate and cyclophosphamide (5). All studies, except for one, used mycophenolate mofetil for the drug formulation. DISEASE PROGRESSION. When compared with placebo, the mean FVC % predicted significantly improved from baseline to 12 and 24months for mycophenolate, with about a 5% difference between the two arms. In addition, the rate of overall improvement in FVC % predicted at 12 and 24months was nearly 2.3-fold higher at both time points in the mycophenolate arm compared with placebo. Similarly, the mean change from baseline in DLCO% predicted was .4% less at both 12 and 24 months for the mycophenolate arm compared with placebo, favouring mycophenolate. There were no differences between mycophenolate and cyclophosphamide in mean change in FVC % predicted or DLCO% predicted at 12 or 24months. There were also no differences between mycophenolate and cyclophosphamide in several measures of radiologic disease, given both treatments led to improvements in radiologic disease individually. In addition, between mycophenolate and placebo, changes in the mRSS favoured mycophenolate. MORTALITY. There was no significant difference in mortality at 24months between mycophenolate and placebo or between mycophenolate and cyclophosphamide. QOL. Significant differences in breathlessness (measured using the TDI score) at all time points, including 24months, favored mycophenolate over placebo. There was no difference in any QoL measure between mycophenolate and cyclophosphamide, although both showed significant improvement separately. ADVERSE EVENTS. There was a nine fold increased risk of anemia in patients treated with mycophenolate versus placebo, but there were no differences in premature discontinuation, serious adverse events, hematuria, leukopenia, neutropenia, or thrombocytopenia. Compared with patients receiving cyclophosphamide, the mycophenolate arm had a 41% lower risk of premature discontinuation of therapy for any reason and 86% lower risk of leukopenia.

Quality of evidence:

The quality of evidence for all outcomes was rated very low, meaning the effect estimates should be interpreted with caution. The primary reasons were due to the majority of outcomes drawing data from indirect evidence. The main study comparing mycophenolate to placebo, for example, was post hoc in nature, with significant differences in baseline characteristics between the groups.

Recommendation 2:

Recommendation 2: We recommend using mycophenolate to treat patients with SSc-ILD (strong recommendation, very low quality evidence).

The committee vote was as follows: strongly in favor to use mycophenolate in people with SSc-ILD: 14 of 18 (78%); conditional recommendation to Use mycophenolate in people with SSc-ILD: 4 of 18 (22%); conditional recommendation to not consider mycophenolate: 0 of 18 (0%); strong recommendation to not consider mycophenolate: 0 of 18 (0%). No guideline participants (0%) abstained from this vote.

- **Question 3: Should patients with SSc-ILD be treated with rituximab?**

Summary of evidence:

A systematic reviewof the evidence identified three RCTs that enrolled patients with SSc and evaluated the effects of rituximab compared with placebo (37–39) (Table E3). However, two of the studies enrolled participants with SSc without a priori confirmation of ILD, thus providing only indirect data on the SSc-ILD population (37, 39). The sample sizes were small, ranging from a total of 14 to 54 patients, and two of the studies were underpowered for the studied outcomes (37, 38). Follow-up for these trials ranged from 24 to 96weeks. Patients received rituximab infusion on Days 1 and 15 and at 6months in one study (37), weekly for four doses at baseline and at 6months in a second study (38), and only weekly for four doses at baseline in a third (39). DISEASE PROGRESSION. Meta-analysis revealed that at 24–48weeks, rituximab attenuated the decline in FVC % predicted by 3.3% when compared with placebo. Individual study and pooled data analyses showed no differences in the mean change in the DLCO % predicted at 24, 24–48, or 96 weeks between the rituximab and placebo arms. Two studies found that rituximab reduced the decline in DLCO (improvement in DLCO, 0.7 to 9.7ml/min/mmHg), whereas one found rituximab increased the decline in DLCO (23.5ml/min/mmHg). There were no significant differences in mean changes in several measures of radiographic disease at 24 or 48weeks, but the estimates are based on small sample sizes. Patients with SSc-ILD who received rituximab had larger decline in them RSS at 24–48weeks by 7 points. MORTALITY. There were no significant differences at 24weeks between the rituximab and placebo arms for mortality. QOL. Individual study and pooled data analyses showed no differences between the rituximab and placebo arms for the Short Form36 bodily pain and general health question subsets or the HAQ-DI scores. ADVERSE EVENTS. No significant differences in adverse events were noted between the rituximab and placebo arms at 24weeks (diarrhea, enterocolitis, gastroesophageal reflux disease, mucositis, respiratory tract infection, arthralgia, decreased neutrophil count, dermatitis, increased C-reactive protein, skin ulcerations and pulmonary valve disease) or 96weeks (blood and lymphatic disorders, infections and infestations, neoplasm, reproductive and

breast, or vascular disorders). Similarly, no differences at 24 weeks were present for any adverse event, serious adverse event, or serious adverse event leading to treatment withdrawal.

Quality of evidence:

The quality of evidence for study outcomes was very low as defined by the GRADE approach, because of risk of bias (premature closing in enrollment), imprecision (limited number of participants/studies contributing to the findings, different rituximab dosing between studies), and indirectness (ILD not determined a priori in the participants).

Recommendation 3:

We suggest using rituximab to treat patients with SSc-ILD (conditional recommendation, very low quality evidence).

The committee vote was as follows: strongly in favor to use rituximab in people with SSc-ILD: 1 of 18 (5.6%); conditional recommendation to use rituximab in people with SSc-ILD: 16 of 18 (88.9%); conditional recommendation to not consider rituximab: 0 of 18 (0%); strong recommendation to not consider rituximab: 0 of 18 (0%).One guideline participant (5.6%) abstained from this vote because of insufficient expertise to render a thoughtful judgment.

- **Question 4: Should patients with SSc-ILD be treated with tocilizumab?**

Summary of evidence:

A systematic review of the evidence identified five studies for inclusion: the faSScinate trial (41) and its open-label extension (42), the focuSSced trial (40) and its open-label extension (43), and a post hoc analysis of data from the focuSSced trial (44) (Table E4). The faSScinate trial was a phase 2 RCT that assigned 87 subjects with SSc across five countries to subcutaneous tocilizumab or placebo over 48weeks. The open-label extension was extended to 96weeks and gave tocilizumab to 30 subjects in the original tocilizumab arm and 31 subjects in the original placebo arm. The focuSSced trial was a phase 3 RCT that assigned 210 subjects with SSc across 20 countries to subcutaneous tocilizumab or placebo over 48weeks. The open-label extension extended to 96weeks and gave tocilizumab to 60 subjects in the original tocilizumab arm and 54 subjects in the original placebo arm. The post hoc analysis assessed QILD and quantitative lung fibrosis (QLF) scores on imaging with QILD categorized asmild (.5–10%), moderate (.10–20%), or severe (.20%). For both the faSScinate and focuSSced trials, the presence of ILD was not an inclusion criterion, and change in mRSS was the primary outcome. But in the focuSSced trial, 136 of the 210 participants (65%) were deemed to have SSc-ILD based on a visual read of HRCT by a thoracic radiologist. DISEASE PROGRESSION. The differences in mean absolute change from baseline in FVC between the tocilizumab and placebo arms were 118ml less at 24weeks, 241ml less at 48 weeks, and 128.7ml less at 96 weeks (the latter being the open-label period) in favor of tocilizumab. Similarly, the difference in mean change from baseline to 48weeks in FVC % predicted was 6.5% less in the tocilizumab arm, with a median change of 3.4% less, but at 96 weeks (when the placebo arm was also given tocilizumab) there was no significant difference between the tocilizumab and placebo arms. The risk of FVC % predicted decrease.10% by 48weeks was three times less in the tocilizumab arm, whereas the risk of any increase in the FVC % predicted at 48 weeks was nearly twice as much in the tocilizumab arm compared with placebo. By 96 weeks (when the placebo arm was also given tocilizumab) there were no significant differences in risk for these parameters. In contrast to the above trends, when evaluating data from 48 to 96weeks in the open-label extension period, the mean change in the absolute FVC was 54.9ml less and the mean change in FVC % predicted was 1.3% less in the placebo arm. The mean change in DLCO % predicted from baseline to 48weeks was 1.5% less in the tocilizumab arm, but the difference was not significant at 96weeks. During the interval from 48 to 96weeks, the mean decrease in DLCO% predicted was 5.4% less in the tocilizumab arm. At 48weeks, the change in QILD and QLF scores across all categories favored the tocilizumab group. The mRSS change from baseline at 72 weeks was 4.1 better in the tocilizumab arm when compared with placebo but was 0.8 better in the placebo arm compared with tocilizumab when looking at 48–96weeks in the open-label extension period when the placebo arm was also given tocilizumab. MORTALITY. There was no significant difference in mortality between the tocilizumab and placebo arms at 24, 48, or 96weeks. QOL. At 96 weeks in the open-label study, the mean change from baseline in the 5-D Itch score, HAQ-DI score, FACIT-Fatigue score, and the Patient Global Visual Analog Scale score all favored the placebo group that was transitioned to tocilizumab during the open-label period. ADVERSE EVENTS. At 48 weeks, there were 3.8 fewer hypersensitivity events, 44 fewer overall adverse events, 7.6 fewer adverse events leading to treatment discontinuation, 9.1 fewer infectious serious adverse events, and 27.4 fewer overall serious adverse events, all per 100 patient-years, for tocilizumab compared with the placebo group. In the open-label extension from 48 to 96weeks, the arm that received tocilizumab the full 96 weeks had 96.7 fewer overall adverse events, 5.6 fewer infectious serious adverse events, and 8.6 overall serious adverse events per 100 patient-years. The placebo arm, however, was found to have 10.2 fewer injection site reactions per 100 patient-years at 48weeks and 6.8 fewer hypersensitivity events per 100 patient-years from 48 to 96 weeks.

Quality of evidence:

The quality of evidence was rated as very low for all outcomes. Therefore, the effects summarized should be interpreted with caution, because the committee had low confidence in the estimated effects. The overall very low-quality rating is based on the lowest quality of evidence rating among the critical outcomes disease progression and mortality. The studies included did not a priori document ILDat enrollment and include post hoc and open-label extension studies, leading to indirectness of evidence and imprecision.

Recommendation 4:

We suggest using tocilizumab to treat patients with SSc-ILD (conditional recommendation, very low quality evidence).

The voting by the committee was as follows: strong recommendation for tocilizumab: 0 of 16 (0%); conditional recommendation for tocilizumab: 16 of 16 (100%); conditional recommendation against tocilizumab: 0 of 16 (0%); and strong recommendation against tocilizumab: 0 of 16 (0%). No participants (0%) abstained from voting.

- **Question 5: Should patients with SSc-ILD be treated with nintedanib?**

Summary of evidence:

A systematic review of the evidence identified three studies for inclusion: the safety and efficacy of nintedanib in systemic sclerosis (SENSCIS) trial (46), a post hoc analysis of the SENSCIS trial (47), and a post hoc analysis of the INBUILD trial (48) (Table E5). The SENSCIS trial was a phase 3 RCT that assigned 576 subjects with SSc-ILD across 32 countries to nintedanib or placebo over 52 weeks. Of note, background therapy with mycophenolate was allowed, with about half of the subjects receiving the therapy. The post hoc analysis examined changes in FVC % predicted at categorical ranges, including at 5%, 10%, and by the minimal clinically important difference (MCID) for improvement and worsening of FVC (49). The INBUILD trial was an RCT that assigned 663 subjects with progressive ILD across 15 countries to nintedanib or placebo over 52weeks. The post hoc analysis assessed prespecified subgroups based on ILD diagnosis, from which 39 patients with SSc-ILD were extracted for data analysis. DISEASE PROGRESSION. The annual rate of decline in FVC was 44.5ml less and the decline in FVC % predicted was 1.2% less in the nintedanib arm compared with placebo, based on data from the SENSCIS trial. The absolute change from baseline in FVC was 46.4ml less for the nintedanib arm, with the risks of absolute decline from baseline in FVC of.5% predicted and relative decline in ml of.5%, both about 25% less in the nintedanib arm. When looking at the MCID (49), the nintedanib arm had .20% reduction in risk of FVC decrease>3.3% predicted (the MCID threshold for worsening FVC) and had a 50% increase in risk of FVC increase of >3.0% predicted (the MCID threshold for improvement in FVC). There was no significant difference in them RSS. MORTALITY. There was no significant difference between the nintedanib or placebo arms for all-cause mortality, fatal adverse events, or serious adverse events that included death. However, for composite outcomes of absolute decline in FVC>10% predicted or death at 52weeks and for absolute decline in FVC>10% predicted or between 5% and 10% predicted with DLCO decline>15% predicted or death at 52weeks, the rate was approximately 40% less in the nintedanib arm compared with placebo. QOL. There was no significant difference between the nintedanib or placebo arms for absolute change from baseline in the HAQDI, FACIT-Dyspnea, or SGRQ scores. ADVERSE EVENTS. Nintedanib increased the risk of nausea (2.3 times), vomiting (2.4times), diarrhea (2.4 times), weight loss (2.8 times), and adverse events leading to treatment discontinuation (1.8 times) but decreased the risk of cough as an adverse event by 35%.

Quality of evidence:

The quality of evidence was rated as very low for all outcomes. Therefore, the effects summarized should be interpreted with caution, because the committee had low confidence in the estimated effects. The overall very low quality rating is based on the lowest quality of evidence rating among the critical outcomes disease progression and mortality. Despite the SENSCIS trial being an RCT, the overall evidence quality was downgraded because the only other studies were post hoc analyses, leading to indirectness of evidence and imprecision. In addition, patients in the placebo arm of the SENSCIS trial were not true placebos, as many were receiving background immunosuppressive medications for treatment of SSc-ILD.

Recommendation 5:

We suggest using nintedanib to treat patients with SSc-ILD (conditional recommendation, very low quality evidence).

The voting by the committee was as follows: strong recommendation for nintedanib, 1 of 14 (7%); conditional recommendation for nintedanib, 11 of 14 (79%); conditional recommendation against nintedanib, 1 of 14 (7%); and strong recommendation against nintedanib, 0 of 14 (0%). One participant (7%) abstained from voting, citing insufficient expertise to render a thoughtful judgment.

- **Question 6: Should patients with SSc-ILD be treated with nintedanib plus mycophenolate?**

Summary of evidence:

A systematic review of the evidence identified three studies meeting inclusion criteria (46, 50, 51) (Table E6). One, the SENSCIS trial, was a study that randomized 576 patients with SSc-ILD to nintedanib or placebo (as noted above), but patients who had been on at least 6months of therapy with mycophenolate at a stable dosage were permitted in the trial (46). The second study was a post hoc subgroup analysis of the SENSCIS trial that examined the efficacy and safety of patients treated with mycophenolate and nintedanib (50). This study reported results for four groups— combination therapy, mycophenolate plus placebo, nintedanib plus placebo, and placebo only—and provided the majority of data for the systematic review. The third trial was an open-label extension of the SENSCIS trial, in which all patients were offered 52 weeks of therapy with nintedanib to examine safety and efficacy (51). DISEASE PROGRESSION. Compared with placebo, there was nearly an 80ml and 2.5% lower annual rate of decline in FVC and FVC % predicted, respectively, for combination therapy with nintedanib plus mycophenolate. Similarly, in the combination therapy arm, the risk of absolute decrease from baseline in FVC of.5% predicted and.10% predicted were 50% and 75% less than the placebo arm, respectively. These changes met established MCID thresholds (49). There were no significant differences in the annual rate of decline in FVC or FVC % predicted between combination therapy and mycophenolate or combination therapy and nintedanib, but the risk of FVC decrease from baseline by.5% was about one-third less in the combination therapy arm when compared with either mycophenolate alone or nintedanib alone. There were no differences identified in mRSS between combination therapy with nintedanib plus mycophenolate versus placebo, mycophenolate only, or nintedanib only. MORTALITY. There were no differences in fatal adverse events comparing combination therapy with nintedanib plus mycophenolate to placebo, mycophenolate only, or nintedanib only. QOL. There were no differences identified in SGRQ scores between combination therapy with nintedanib plus mycophenolate to placebo, mycophenolate only, or nintedanib only. ADVERSE EVENTS. Combination therapy was associated with a sevenfold higher risk of decreased appetite, more than 2.5-fold higher risk of diarrhea, and about threefold higher risk of nausea, vomiting, and/or fatigue compared with placebo. Combination therapy was also associated with nearly twice the risk of diarrhea, nausea, and vomiting compared with mycophenolate only. Combination therapy was associated with a 1.65-fold increase in serious adverse events (defined as an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason) compared with mycophenolate only. Adverse event data could not be pooled for the comparison between combination therapy and nintedanib only, but, interestingly, combination therapy was associated with a 60% lower risk of liver test abnormalities compared with nintedanib only.

Quality of evidence:

The quality of evidence for all outcomes was rated as very low, meaning that the committee had very low confidence in the estimated effects. As a result, the effect estimates should be interpreted with caution. There were multiple reasons for the very low quality of evidence. Each outcome was informed by only a single study, leading to imprecision. Furthermore, study design limitations downgraded evidence quality, as the majority of data were informed by a post hoc analysis of an RCT. Finally, although treatment with nintedanib was randomized, therapy with mycophenolate was not randomized, and those patients receiving background therapy with mycophenolate had several differences in demographics compared with patients not on background mycophenolate therapy (50).

Recommendation 6:

We suggest using the combination of nintedanib plus mycophenolate to treat patients with SSc-ILD (conditional recommendation, very low quality evidence).

The voting by the committee was as follows: strong recommendation for nintedanib plus mycophenolate, 1 of 14 (7%); conditional recommendation for nintedanib plus mycophenolate, 11 of 14 (79%); conditional recommendation against nintedanib plus mycophenolate, 0 of 14 (0%); and strong recommendation against nintedanib plus mycophenolate, 0 of 14 (0%). Two participants (14%) abstained from voting, citing insufficient expertise to render a thoughtful judgment.

- **Question 7: Should patients with SSc-ILD be treated with pirfenidone?**

Summary of evidence:

A systematic review of the evidence identified one RCT evaluating the use of pirfenidone in SSc-ILD (52) (Table E7). This study, however, was underpowered for the proposed outcomes, as it enrolled only 53% of the total planned participants (n = 34) because of limited availability of pirfenidone as a study drug. In addition, only 6% of the total participants received the pirfenidone target dose of 2,400mg/d. A majority of participants were receiving background therapy, mostly mycophenolate mofetil, azathioprine, and prednisolone, which may have confounded the effect of pirfenidone on proposed outcomes. Although SSc-ILD was confirmed before enrollment, the extent of the ILD is not known. It is mentioned, however, that the majority of participants (61.7%) had nonspecific interstitial pneumonia, with the remaining (32.2%) having a UIP pattern on the HRCT of the chest. DISEASE PROGRESSION. There were no significant differences between pirfenidone

and placebo for change from baseline in FVC % predicted, 6-minute-walk distance, or mRSS. MORTALITY. Mortality was not reported in this study. QOL. There was no difference at 24weeks between pirfenidone and placebo in the median change from baseline in the TDI scores. ADVERSE EVENTS. There was no difference at 24weeks between pirfenidone and placebo for any adverse event (including nausea, vomiting, diarrhea, rashes, loss of appetite, constitutional symptoms, thrombocytopenia, or elevation of transaminases).

Quality of evidence:

The quality of evidence for both critical and important outcomes was very low as defined by the GRADE approach, due primarily to study bias (low enrollment numbers owing to lack of pirfenidone availability as a study drug) and imprecision (limited number of participants/studies contributing to the findings, and lack of uniform distribution of pirfenidone dosing among the participants).

Recommendation 7:

We recommend further research into the safety and efficacy of pirfenidone to treat patients with SSc-ILD.

The voting by the committee was as follows: strong recommendation for pirfenidone, 0 of 13 (0%); conditional recommendation for pirfenidone, 0 of 13 (0%); conditional recommendation against pirfenidone, 2 of 13 (15%); and strong recommendation against pirfenidone, 0 of 13 (0%). Eleven participants (85%) abstained from voting, citing insufficient evidence to render a thoughtful judgment.

- **Question 8: Should patients with SSc-ILD be treated with pirfenidone plus mycophenolate?**

Summary of evidence:

A systematic review of the evidence identified one published study, the LOTUSS trial (53), and one abstract from the SLS III trial (54) for inclusion (Table E8). The LOTUSS trial (53) was an open-label phase 2 study of 63 patients with SSc-ILD monitored over 16 weeks assessing safety and tolerability of pirfenidone. Patients were not randomized to mycophenolate, but 63.5% of patients were concomitantly on it, so the data analyzed was post hoc. The baseline mycophenolate dose varied between participants, and 20% of patients were on steroids and other antirheumatic medications. In addition, changes in lung function were exploratory outcomes, not primary. The abstract described the results of the SLS III RCT that compared the treatment with combined pirfenidone and mycophenolate to mycophenolate plus placebo, with the primary outcome being change in lung function at the end of 18 months. The study was aborted due to inability to enroll the intended sample size and had just enrolled 51 of the targeted 150 participants, so the results noted in the abstract were from a very small sample size and thus the study was underpowered (54). While the abstract of the SLS III study does not include many secondary outcomes that are anticipated to be published in the full report in the near future, the published primary outcomes in the abstract were also our critical outcomes of interest for decision-making. DISEASE PROGRESSION. No significant difference in FVC % predicted or DLCO% predicted was observed between the combination pirfenidone plus mycophenolate arm and pirfenidone alone. There were also no differences between the combination pirfenidone plus mycophenolate arm and the mycophenolate and placebo arms in FVC % predicted or time duration to.3% increase in FVC % predicted at 18months. MORTALITY. Mortality was not reported in either the LOTUSS trial or the SLS III abstract. QOL. The LOTUSS trial found that compared with mycophenolate alone, the combination of pirfenidone plus mycophenolate showed a 2-point improvement in the TDI score at 16 weeks, but there was no significant difference in HAQ-DI scores. ADVERSE EVENTS. The LOTUSS trial did not observe any significant differences in severe adverse events, withdrawal because of severe adverse events, or infections at 16 weeks between combination therapy and the pirfenidone-only arm.

Quality of evidence:

The quality of evidence was very low by the GRADE approach because of bias (premature closure of enrollment), imprecision (limited number of participants/studies contributing to the findings, lack of uniform distribution of mycophenolate treatment in the pirfenidone and mycophenolate participants), and indirectness of evidence (post hoc analysis of data).

Recommendation 8:

We recommend further research into the safety and efficacy of pirfenidone plus mycophenolate combination therapy to treat patients with SSc-ILD.

The voting by the committee was as follows: strong recommendation for pirfenidone plus mycophenolate, 0 of 13 (0%); conditional recommendation for pirfenidone plus mycophenolate, 0 of 13 (0%); conditional recommendation against pirfenidone plus mycophenolate, 1 of 13 (8%); and strong recommendation against pirfenidone plus mycophenolate, 0 of 13 (0%). Twelve participants (92%) abstained from voting, citing insufficient evidence to render a thoughtful judgment.

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Del Galdo F et al., 2024 [1].

European Alliance of Associations for Rheumatology

EULAR recommendations for the treatment of systemic sclerosis: 2023 update

Methodik

Methodikeranmerkung: Es handelt sich um ein Update der LL „EULAR recommendations for treatment of systemic sclerosis (SSc)“ aus dem Jahr 2017.

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu.

Recherche/Suchzeitraum:

- Embase, pubmed and Cochrane Library, siehe: https://ard.bmj.com/content/82/Suppl_1/973
- from 1 January 2015 to 31 March 2023

LoE/GoR

For each question, reviewers provided a summary of the up-to- date knowledge to the task force, specifying the level of evidence (LoE) (1–5) according to CEBM criteria and suggesting a preliminary grade of recommendation (SoR, strength of recommendation).

Sonstige methodische Hinweise

Empfehlungen

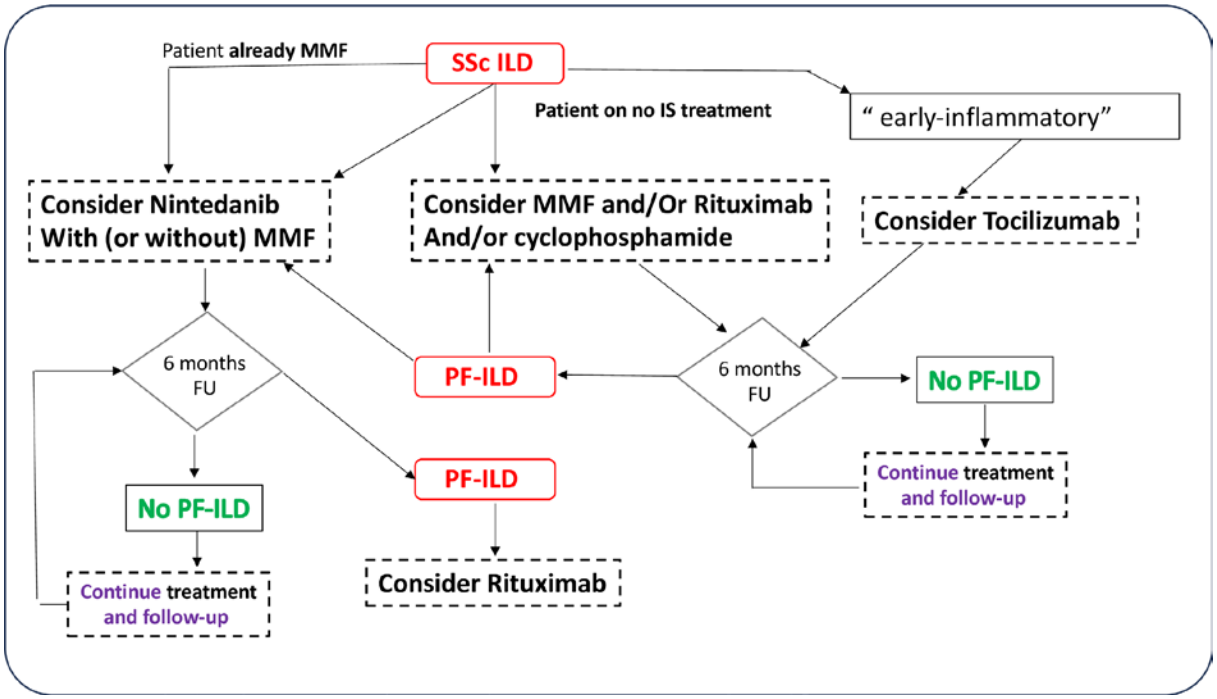

Figure 1: Treatment flow chart the evidence informing the recommendations for treatment of SSc interstitial lung disease (ILD). ILD, interstitial lung disease; IS, immune suppressive; MMF, mycophenolate mofetil; PF, progressive fibrosing; SSc, systemic sclerosis.

Table 1 Updates of EULAR recommendations for the treatment of systemic sclerosis

Organ involvement	Recommendation	LoE	SoR	LoA (SD)	% LoA>8
ILD	MMF (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for the treatment of SSc-ILD*	1a	A	8.1 (2.8)	88
	Nintedanib should be considered alone or in combination with MMF for the treatment of SSc-ILD*	1a	A	8.5 (2.5)	84
	Tocilizumab should be considered for the treatment of SSc-ILD*	1b	B	7.8 (2.8)	76

*Substantially new recommendations compared with 2017 update.
EULAR, European Alliance of Associations for Rheumatology; GERD, gastro-oesophageal reflux disease; HSCT, haematopoietic stem cell transplantation; ILD, interstitial lung disease; LoA, level of agreement; LoE, level of evidence; PAH, pulmonary artery hypertension; RP, Raynaud's phenomenon; SoR, strength of recommendation; SSc, systemic sclerosis.

Hintergrund:

- **Mycophenolate mofetil, cyclophosphamide or rituximab**

The SLS II compared a continuous 24-month course of MMF to a 12-month course of oral cyclophosphamide (followed by 12 months of placebo) in an RCT of SSc-ILD patients (see Tashkin *et al*[43] and online supplemental extended results). Each treatment group showed significant improvement in % predicted FVC at 24 months, 2.19% (95% CI 0.53% to 3.84%) for the MMF group and 2.88% (95% CI 1.19% to 4.58%) for the cyclophosphamide group. MMF was better tolerated than cyclophosphamide based on the time to patient withdrawal, the number of treatment failures and incidence of leucopoenia and thrombocytopaenia. The task force noted that the SLS studies[43 44] investigated oral cyclophosphamide and there were insufficient data to compare the risk/benefit ratio of oral versus intravenous route for the treatment of SSc-ILD. Based on these and other consistent data (online supplemental extended results)[43 44 54], the task force agreed to recommend both MMF and cyclophosphamide for the treatment of SSc-ILD (A). The RECITAL trial compared rituximab to intravenous cyclophosphamide in a basket design including ILD related to 3 CTDs (97 patients including 37 with SSc) (see online supplemental extended results).[55] At week 24, both groups showed improvement with unadjusted mean gain from baseline in FVC of 99 mL (SD 329; relative change 4.35% (SD 15.67)) in the cyclophosphamide group and 97 mL (234; 4.31% (11.80)) in the rituximab group. More adverse events were reported in the cyclophosphamide group (646 events) than in the rituximab group (445 events). Further, in

the phase 2 DESIRES clinical trial (see online supplemental extended results[47]), the predicted FVC at 24 weeks compared with baseline was significantly improved in the rituximab group compared with the placebo group (0.09% vs –2.87%; difference 2.96% (95% CI 0.08% to 5.84%); p=0.044). Open-label studies and meta-analysis of 20 studies further supported the beneficial effects of rituximab on FVC in SSc-ILD (see online supplemental extended results)[56 57], therefore the task force recommended that rituximab should be considered for the treatment of SSc-ILD.

- **Nintedanib**

Since the last update of the recommendations, the largest clinical trial ever conducted in SSc investigated the effects of the tyrosine-kinase inhibitor nintedanib in SSC ILD, SENSCIS (see online supplemental extended results).[58 59] While several other tyrosine kinase inhibitors have been tested in proof-of- concept studies, no other molecule has been ever evaluated as a disease-modifying agent for SSc or SSc-ILD in a large international multicentre phase III trial. In SENSCIS, 576 SSc-ILD patients were randomly assigned to receive 150 mg of nintedanib, administered orally twice daily or placebo. In the primary end-point analysis, the adjusted annual rate of change in FVC was −52.4 mL per year in the nintedanib group and −93.3 mL per year in the placebo group (p=0.04). Other prespecified endpoints were not met, and adverse events were higher in the nintedanib group (16.0% vs 8.7%). Diarrhoea, the most common adverse event, was reported in 75.7% of the patients in the nintedanib group (vs 31.6% in the placebo group). The 52 weeks open-label extension study (SENSICS-ON) confirmed the similar changes in FVC and the safety profile seen in SENSCIS.[60] Importantly, patients included in the SENSCIS trial were stratified for the use of MMF and preplanned subanalysis included evaluation of the primary endpoint by MMF use.[61] The relative treatment effect of nintedanib was similar (40% for those taking MMF at baseline and 46% for those not using) and consistent with that observed in the overall population (44%). The treatment effect of nintedanib on the annual rate of FVC decline was numerically greater in participants who were not taking MMF at baseline (difference: 55.4 mL per year (95% CI 2.3 to 108.5)) than in those who were taking MMF (26.3 mL per year (–27.9 to 80.6). The adverse event profile of nintedanib was generally similar with or without MMF. Very importantly, the INBUILD trial further assessed nintedanib in a basket population of progressive fibrosing ILD (PF-ILD). In this phase 3 trial, patients were assigned to receive nintedanib (150 mg two times per day) or placebo while background immunosuppressants at inclusion were not allowed.[62] It is important to note that the inclusion criteria of INBUILD built the foundation for the definition of PF-ILD, formally only agreed on consensus in 2020.[63] Among 170 patients with autoimmune disease-related ILDs (including 39 SSc-ILD), the rate of decline in FVC over 52 weeks was −75.9 mL/year with nintedanib vs −178.6 mL/year with placebo (difference 102.7 mL/year (95% CI 23.2 to 182.2); nominal p=0.012). Considering the results of the SENSCIS and INBUILD trials and the results concerning those concomitantly treated with mycophenolate, the task force recommended that nintedanib should be considered alone or in combination with MMF for the treatment of SSc ILD (A)

- **Tocilizumab**

Within the two trials having mRSS as primary endpoint discussed above, changes in FVC were assessed as secondary endpoint (see online supplemental extended results).[50–52] The 24-week study clearly showed significantly smaller decrease in FVC for tocilizumab than for placebo (tocilizumab –34 mL vs placebo –171 mL; p=0.0368).[50] In the phase 3 trial, the 48-week LSM change from baseline in FVC% predicted was –4.6 in the placebo group and –0.4 in the tocilizumab group (difference 4.2 (95% CI 2.0 to 6.4); nominal p=0.0002).[51] Based on these data, the FDA approved the use of tocilizumab for the treatment of SSc-ILD. The task force acknowledged that ILD was not the primary objective of both these tocilizumab trials, although it was prespecified as secondary outcome in the phase 3 trial. As well, the magnitude of effect between the two arms was large although the drug was investigated with no background treatment in an early, inflammatory population. As a result of discussion, the task force agreed to recommend that tocilizumab should be considered for the treatment of SSc-ILD. A diagram summarising different options for SSc-ILD treatment is shown in figure 1.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2024) am 23.12.2024

#	Suchschritt
1	[mh "Lung Diseases, Interstitial"]
2	(interstitial NEAR/3 (lung OR pneumon* OR pulmon*)):ti,ab,kw
3	(diffuse NEAR/3 parenchym*):ti,ab,kw
4	((extrinsic AND allergic AND alveolit*) OR (hypersensitiv* NEAR/3 pneumonit*)):ti,ab,kw
5	((bird* OR pigeon* OR budgerigar* OR farmer* OR avian*) NEAR/3 lung):ti,ab,kw
6	((goodpasture* NEAR/3 (syndrom* OR disease*)) OR (lung NEAR/3 purpura)):ti,ab,kw
7	(pneumoconios* OR bagassos* OR anthracos* OR asbestos* OR beryllios* OR byssinos* OR (caplan NEXT syndrome) OR sideros* OR silicos*):ti,ab,kw
8	(radiation NEAR/3 (pneumon* OR fibros*)):ti,ab,kw
9	((sarcoidos* OR fibros*) NEAR/3 (pulmon* OR lung*)):ti,ab,kw
10	{OR #1-#9}
11	[mh "scleroderma, Systemic"]
12	(systemic NEXT (scleroderma* OR scleros*)):ti,ab,kw
13	[mh Dermatomyositis]
14	(dermatomyosit* OR polymyosit*):ti,ab,kw
15	[mh "Arthritis, Rheumatoid"]
16	(rheumatoid NEAR/3 arthrit*):ti,ab,kw
17	[mh "Lupus Erythematosus, Systemic"]
18	(lupus NEAR/3 erythematos*):ti,ab,kw
19	{OR #11-#18}
20	(lung OR pulmon* OR pneumon*):ti,ab,kw AND #19
21	{OR #10, #20}
22	#21 with Cochrane Library publication date from Dec 2019 to present

Leitlinien und systematische Reviews in PubMed am 23.12.2024

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchschritt
	Leitlinien
1	Lung Diseases, Interstitial[mh]
2	interstitial[tiab] AND (lung[tiab] OR pneumon*[tiab] OR pulmon*[tiab])
3	diffuse[tiab] AND parenchym*[tiab] AND lung[tiab]
4	(extrinsic[tiab] AND allergic[tiab] AND alveolit*[tiab]) OR (hypersensitiv*[tiab] AND pneumonit*[tiab])
5	(bird*[tiab] OR pigeon*[tiab] OR budgerigar*[tiab] OR farmer*[tiab] OR avian*[tiab]) AND lung[tiab]
6	(goodpasture*[tiab] AND (syndrom*[tiab] OR disease*)) OR (lung[tiab] AND purpura[tiab])
7	pneumoconios*[tiab] OR bagassos*[tiab] OR anthracos*[tiab] OR asbestos*[tiab] OR beryllios*[tiab] OR byssinos*[tiab] OR “caplan syndrome”[tiab] OR sideros*[tiab] OR silicos*[tiab]
8	radiation[tiab] AND (pneumon*[tiab] OR fibros*[tiab])
9	(sarcoidos*[tiab] OR fibros*[tiab]) AND (pulmon*[tiab] OR lung*[tiab])
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	Scleroderma, Systemic[mh]
12	systemic scleroderma*[tiab] OR systemic scleros*[tiab]
13	Dermatomyositis[mh]
14	dermatomyosit*[tiab] OR polymyosit*[tiab]
15	Arthritis, Rheumatoid[mh]
16	rheumatoid[tiab] AND arthrit*[tiab]
17	Lupus Erythematosus, Systemic[mh]
18	lupus[tiab] AND erythematos*[tiab]
19	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20	lung[tiab] OR pulmon*[tiab] OR pneumon*[tiab]
21	#19 AND #20
22	#10 OR #21
23	(#22) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])

#	Suchschritt
24	((((#23) AND ("2019/12/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	systematische Reviews
25	(#10) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
26	(((#25) AND ("2019/12/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))) NOT ("retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "preprint"[Publication Type])
	systematische Reviews ohne Leitlinien
27	(#26) NOT (#24)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 02.01.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-320-z

Verfasser	
Name der Institution	1) Gesellschaft für Kinderrheumatologie 2) Gesellschaft für pädiatrische Pneumologie
Datum der Erstellung	28. Januar 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
… indicated in adults, adolescents and children aged 6 years and older for the treatment of systemic sclerosis associated interstitial lung disease (SSc ILD). Inoffizielle Übersetzung: „…ist angezeigt für die Behandlung von interstitiellen Lungenerkrankungen im Zusammenhang mit systemischer Sklerose (SSc ILD) bei Erwachsenen, Jugendlichen und Kindern ab 6 Jahren." – Hier zu betrachten Kinder und Jugendliche von 6 bis 17 Jahren.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Der Behandlungsstandard der interstitiellen Lungenerkrankung im Zusammenhang mit der systemischen Sklerose (SSc ILD) bei Erwachsenen, Jugendlichen und Kindern ab 6 Jahren orientiert sich einerseits an der Gesamtbehandlung Este Stufe der Therapie ist Mycophenolat (1250-1500 mg/m2/Körperoberfläche /Tag) (Ausweichpräparat Cyclophosphamid) (Foeldvari et al 2024). Bei nicht ausreichendes Ansprechen nach 3-4 Monaten (Treat to target Konzept) zusätzlich Tociliumab in der Dosierung, wie bei juvenilen systemischen Arthritis. Rituximab ist eine alternative zu Tocilizumab (1). Bei nicht ausreichenden Ansprechen oder Progression zusätzlich Nintedanib (2). Bei nicht ausreichenden Ansprechen und schnellen Progression CAR T Zell Therapie (1). Therapiekonzept basiert auf Foeldvari et al. "Best clinical practice in the treatment of juvenile systemic sclerosis: expert panel guidance - The result of the International Hamburg Consensus Meeting December 2022." First line therapy in jSSc ILD is MMF or Cyclophosphamide ± in combination the systemic CS. MMF is preferred over cyclophosphamide due to better safety profile. Additional agents to consider are Tocilizumab, Rituximab and Ninetadanib
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

	1st Line	2nd Line	3rd Line	Supportive
Interstitial Lung Disease	Mycophenolate mofetil Cyclophosphamide Tocilizumab Corticosteroids	Nintedanib Rituximab	Autologous hematopoietic stem cell transplantation	Aggressively treat GERD Keep vaccines up to date Pulmonary rehabilitation • Inspiratory muscle training

Referenzliste:

1. Foeldvari I, Torok K, Anton Lopez J, Blakley M, Constantin T, et.al. Best clinical practice in the treatment of juvenile systemic sclerosis: expert panel guidance - The result of the International Hamburg Consensus Meeting December 2022. Expert Review of Clinical Immunology. 2024.

2. Deterding R, Young LR, DeBoer EM, Warburton D, Cunningham S, Schwerk N, et al. Nintedanib in children and adolescents with fibrosing interstitial lung diseases. Eur Respir J. 2023;61(2).