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: 2020-B-150z Nintedanib

Stand: Juli 2020

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

Nintedanib
zur Behandlung einer interstitiellen Lungenerkrankung bei Erwachsenen

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 *(Beschluss vom 17. Oktober 2019))* • (Pirfenidon *(Beschluss vom 15. März 2012))*
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®	<u>Anwendungsgebiet laut Fachinformation:</u> Ofev wird angewendet bei Erwachsenen zur Behandlung der idiopathischen Lungenfibrose (IPF) Ofev wird angewendet zur Behandlung einer interstitiellen Lungenerkrankung bei Erwachsenen mit systemischer Sklerose (SSc-ILD). (Stand FI: April 2020) <u>Anwendungsgebiet laut Positive Opinion vom 28.05.2020:</u> Ofev is indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype.
Methylprednisolon H02AB04 Methylprednisolon Jenapharm®	<u>Bronchial- und Lungenkrankheiten</u> […] – 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) (Stand FI: April 2018)
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) […] (Stand FI: September 2017)
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)

	[…] (Stand FI: September 2017)
Pirfenidon L04AX05 Esbriet®	Esbriet wird angewendet bei Erwachsenen zur Behandlung von leichter bis mittelschwerer idiopathischer pulmonaler Fibrose (IPF). (Stand FI: April 2018)

Quellen: AMIS-Datenbank, Fachinformationen (Stand: Juli 2020)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-150z (Nintedanib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	15. Juli 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CYC	cyclophosphamide
DM	dermatomyositis
ECMO	Extracorporeal Membrane Oxygenation
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MDA5 (+)	Melanoma Differentiation-Associated Gene 5-positive
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
RPILD	progressive interstitial lung disease
SLS	Scleroderma Lung Study
SSc	systemic sclerosis
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Anwendungsgebiet 1:
„Ofev wird angewendet zur Behandlung einer interstitiellen Lungenerkrankung bei Erwachsenen mit systemischer Sklerose (SSc-ILD).“

Anwendungsgebiet 2:

„Ofev is indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype.”

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *interstitielle Lungenerkrankungen* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 26.06.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 819 Quellen. 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 Quellen 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 4 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2020 [1].

Richtlinie des Gemeinsamen Bundesausschusses über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung (Heilmittel-Richtlinie/HeilM-RL) in der Fassung vom 19. Mai 2011; veröffentlicht im Bundesanzeiger Nr. 96 (S. 2247) vom 30. Juni 2011; in Kraft getreten am 1. Juli 2011; zuletzt geändert am 20. Februar 2020; veröffentlicht im Bundesanzeiger BAnz AT 20.05.2020 B2; in Kraft getreten am 1. Juli 2020

Zweiter Teil: Zuordnung der Heilmittel zu IndikationenZweckmäßige Vergleichstherapie

3 Erkrankungen der inneren Organe

Indikation		Ziel der Physikalischen Therapie	Heilmittelverordnung im Regelfall	
Diagnosengruppe	Leitsymptomatik: Funktionelle/strukturelle Schädigung		A. vorrangige Heilmittel B. optionale Heilmittel *C. ergänzende Heilmittel* D. standardisierte Heilmittelkombinationen	Verordnungsmengen je Diagnose ---------- weitere Hinweise
AT1 **Störungen der Atmung** • **mit prognostisch kurzzeitigem Behandlungsbedarf** z. B. bei - Pneumonie, Pleuritis - Asthma bronchiale - Lungenfibrose - Thoraxoperation	**a** Atemnot, auch anfallsweise auftretend, ggf. auch Auswurf	Erlernen einer physiologischen Atmung, Verbesserung der Thoraxbeweglichkeit einschl. der Atemhilfsmuskulatur, der Expektoration und Hustentechnik	**A. KG (Atemtherapie)** *C. KMT/Wärmetherapie (insbesondere heiße Rolle)/Inhalation*	**Erst-VO:** • bis zu 6x/VO **Gesamtverordnungsmenge des Regelfalls:** • bis zu 6 Einheiten **Frequenzempfehlung:** • mind. 2x wöchentlich **Ziel:** Erlernen eines Eigenübungsprogrammes
	b Auswurf	Sekretlockerung, Sekretverflüssigung, Entzündungshemmung	**A. Inhalation**	
	c Husten, obstruktive Ventilationsstörungen	Spasmolyse der Bronchialmuskulatur	**A. BGM** *C. Inhalation/Wärmetherapie (insbesondere heiße Rolle)*	

AT2
Störungen der Atmung
• **mit prognostisch längerdauerndem Behandlungsbedarf**
z. B. bei
- ZNS-Erkrankungen
- Erkrankungen des Rückenmarks
- bei chronisch persistierenden Atemwegserkrankungen wie
  - Lungenfibrosen
  - chronischer Bronchitis
  - chronischem Emphysem
	a
	Atemnot, auch anfallsweise auftretend, ggf. auch Auswurf
		Erlernen einer physiologischen Atmung, Verbesserung der Thoraxbeweglichkeit einschl. der Atemhilfsmuskulatur, der Expektoration und Hustentechnik	**A. KG (Atemtherapie)**
			C. KMT/Wärmetherapie/Inhalation
				Erst-VO:
				• bis zu 6x/VO
				Folge-VO:
				• bis zu 6x/VO
				Gesamtverordnungsmenge des Regelfalls:
				• bis zu 18 Einheiten
				davon für **Massagetechniken**
				bis zu 10 Einheiten
				Frequenzempfehlung:
				• mind. 1x wöchentlich
				Ziel:
				Erlernen eines Eigenübungsprogrammes
				Hinweise:
				Sofern im Einzelfall verlaufsabhängig unmittelbar ein Wechsel von **AT1** zu **AT2** medizinisch begründet ist, ist die bereits zu **AT1** erfolgte Verordnungsmenge auf die Gesamtverordnungsmenge von **AT2** anzurechnen.
				Ein Wechsel von **AT2** zu **AT1** ist nicht möglich.

	b Auswurf	Sekretlockerung, Sekretverflüssigung, Entzündungshemmung	**A. Inhalation**	
	c Husten, obstruktive Ventilationsstörungen	Spasmolyse der Bronchialmuskulatur	**A. BGM** *C. Inhalation/Wärmetherapie (insbesondere heiße Rolle)*	

3.2 Cochrane Reviews

Es konnten keine relevanten Quellen identifiziert werden.

3.3 Systematische Reviews

Es konnten keine relevanten Quellen identifiziert werden.

3.4 Leitlinien

Hinweis: Die Empfehlungen der folgend dargestellten Leitlinie beziehen sich auf das AWG 1: „Ofev wird angewendet zur Behandlung einer interstitiellen Lungenerkrankung bei Erwachsenen mit systemischer Sklerose (SSc-ILD)“. Es wurden alle Empfehlungen, unabhängig vom Zulassungsstatus, zur Therapie der betreffeneden Indikation dargestellt.

Kowal-Bielecka O et al., 2017 [2].
European League against Rheumatism (EULAR)
Update of EULAR recommendations for the treatment of systemic sclerosis

Zielsetzung/Fragestellung

to update the 2009 European League against Rheumatism (EULAR) recommendations for the treatment of systemic sclerosis (SSc), with attention to new therapeutic questions

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: 32 clinical experts from Europe and the USA, 2 patients nominated by the pan-European patient association for SSc (systemic sclerosis) and 1 clinical epidemiologist
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: Potential conflicts of interest were declared by all participants. There was no involvement of third parties in the entire process of making these recommendations.
- Formulierung klinischer Fragestellungen nach PICO
- Systematische Suche, Auswahl und Bewertung der Evidenz
- Formale Konsensusprozesse beschrieben
- externes Begutachtungsverfahren nicht dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt
- Regelmäßige Überprüfung der LL nicht beschrieben, da es sich jedoch um eine Aktualisierung einer Vorgängerversion handelt, wird davon ausgegangen, dass Aktualität der LL gesichert ist

Recherche/Suchzeitraum:

For new clinical questions, the literature search was performed on all articles published between 1966 and, as agreed by the panel, until 30 September 2014 in PubMed, EMBASE, the Cochrane Database for meta-analyses and the Cochrane Controlled Trials Register as well as the 2012 and 2013 EULAR and American College of Rheumatology (ACR) congress abstract archives. For clinical questions already included in the existing recommendations the same strategy was followed, searching from February 2007 to 30 September 2014. A standardised search strategy was used for all clinical questions.

LoE, GoR:

- GRADE

Sonstige methodische Hinweise

- externes Begutachtungsverfahren nicht dargelegt
- Regelmäßige Überprüfung der LL nicht beschrieben, da es sich jedoch um eine Aktualisierung einer Vorgängerversion handelt, wird davon ausgegangen, dass Aktualität der LL gesichert ist.

Empfehlungen: „Skin and lung disease“

Empfehlung (10) In view of the results from two high-quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-related interstitial lung disease (SSc-ILD), in particular for patients with SSc with progressive ILD (strength of recommendation: A).

The evidence regarding efficacy of CYC (cyclophosphamide) in SSc-ILD results mainly from two high-quality (Jadad score 5) RCTs and their subanalyses.[58 59] The first trial (Scleroderma Lung Study (SLS)), involving 158 patients with SSc with active alveolitis, demonstrated that CYC given orally at a dose of 1–2 mg/kg/day improved lung volumes, dyspnoea score and quality of life over 12 months compared with placebo.[58] The placebo-corrected mean (95% CI) improvement in forced vital capacity (FVC) and total lung capacity (TLC) was 2.5% (0.3%–4.8%) and 4.1% (0.5%–7.7%), respectively (p=0.03 for both measures). No significant effect on diffusing lung capacity for carbon monoxide (DLCO) could be demonstrated. CYC also improved the transitional dyspnoea index, the health assessment questionnaire (HAQ) disability index and the vitality and health-transition domains of the Short-Form 36 (p<0.05 vs placebo for all measures).[58] Subanalysis of the SLS revealed that CYC therapy was also associated with significant improvement in high resolution computed tomography (HRCT) score.[60] Extension of the SLS study showed that the FVC continued to improve after cessation of CYC treatment reaching a maximum at 18 months: 6 months after stopping CYC therapy (mean FVC difference vs placebo:subanalyses.58 59 The first trial 4,16%, p=0.01).[61] The beneficial effects of CYC disappeared 1 year after CYC was terminated. The effect of CYC was greater in patients with more severe lung and/or skin disease.[61 62] The mean FVC improvement in patients with baseline FVC lower than 70% of predicted was 4.62% at 12 months and 6.8% at 18 months (p<0.006 for both time points), while in patients with baseline FVC>70% of predicted the mean treatment effect was 0.55% at 12 months and 2.67% 18 months (p>0.05 for both time points). Another subanalysis of the SLS study revealed that the HRCT score and skin disease were independent predictors of response to CYC therapy.[62] In patients with 50% or more of any lung zone involved by reticular infiltrates on HRCT and/or with mRSS of at least 23/51, the CYC treatment effect was 9.81% at 18 months (p<0.001) versus no treatment effect (0.58% difference, p>0.05) in patients with less severe HRCT findings and a lower mRSS at baseline.

The second trial evaluated CYC (intravenously at a dose of 600 mg/m2/month) compared with placebo in 45 patients with SSc-ILD.59 Active treatment included six infusions of CYC given at 4-week intervals followed by oral azathioprine (2.5 mg/kg/day) or placebo for 6 months. Prednisolone (20 mg on alternate days) was co-administered in the active treatment group. The mean adjusted between-group difference in FVC was 4.2% in favour of CYC, which just missed statistical significance (p=0.08). The lung diffusing capacity for carbon monoxide and other outcome measures did not improve.[59] Considering the results of both RCTs and the fact that the benefit of CYC was mainly due to inhibition of progression of SSc-ILD, the experts recommend that CYC therapy should be considered in particular in patients with progressive lung disease. As in the previous 2009 recommendations there was unanimous consensus of

the experts with respect to the CYC dose and duration of treatment to be tailored individually dependent on the clinical condition and response. Potential risks of bone marrow suppression, teratogenicity, gonadal failure and haemorrhagic cystitis must be always considered.[63]

Referenzen aus Leitlinien
58 Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.
59 Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54:3962–70.
60 Goldin J, Elashoff R, Kim HJ, et al. Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study. Chest 2009;136:1333–40.
61 Tashkin DP, Elashoff R, Clements PJ, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026–34.
62 Roth MD, Tseng CH, Clements PJ, et al. Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease. Arthritis Rheum 2011;63:2797–808.
63 Lynch JP III, McCune WJ. Immunosuppressive and cytotoxic pharmacotherapy for pulmonary disorders. Am J Respir Crit Care Med 1997;155:395–420.

Hinweis: Die Empfehlungen der folgend dargestellten Leitlinien beziehen sich auf das AWG 2: „Ofev is indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype.“ Es wurden alle Empfehlungen, unabhängig vom Zulassungsstatus, zur Therapie der betreffeneden Indikation dargestellt.

Romero-Bueno F et al., 2020 [4].

Recommendations for the treatment of anti-melanoma differentiationassociated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease

Zielsetzung/Fragestellung

to develop evidence-based recommendations for the treatment of rapidly progressive interstitial lung disease (RPILD) associated with the anti-Melanoma Differentiation-Associated Gene 5-positive dermatomyositis (DM) syndrome.

Methodik

Grundlage der Leitlinie

- Gremium bestehend aus Experten und Expertinnen unterschiedlicher Professionen, Betroffene waren nicht beteiligt
- Interessenkonflikte dargelegt
- finanzielle Unterstützung durch: This project was supported by Spanish Rheumatology Society and Spanish Society of Internal Medicine (GEAS, Study Group on Autoimmune Diseases).
- Formulierung von Fragestellungen nach PICO
- Systematische Suche in PubMed (MEDLINE), EMBASE (Elsevier), and Cochrane Library (Wiley Online) until April 2018
- Auswahl und Bewertung der Evidenz: Evaluation of the quality of the studies and summary of the evidence for each question was performed using the critical reading tool of the Agency for Healthcare Technology Assessment of the Basque Country (OSTEBA)
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- PubMed (MEDLINE), EMBASE (Elsevier), and Cochrane Library (Wiley Online) until April 2018
- expert group identified some studies which had been published till July 2019 and were included in the evidence corpus

LoE/GoR:

determination of the evidence levels and the recommendations grade was based on SIGN methodology (Scottish Intercollegiate Guidelines Network)

	Levels of evidence
1++	High quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with little risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high bias risk.
2++	High quality systematic reviews of cohort or case-control studies. Cohort or case-control studies with very low risk of bias and with high probability of establishing a causal relationship. Studies classified as 1-
2+	Well conducted cohort or case-control studies with low risk of bias and a moderate probability of establishing a causal relationship..
2-	Cohort or case-control studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies such as case reports and case series.
4	Expert opinion.

and 2- must not be used in the process of developing recommendations due to their high potential for bias.

	Grades of recommendation
A	At least one meta-analysis, systematic review or clinical trial rated as 1++ directly applicable to the target population of the guide; or a body of evidence consisting of studies rated as 1+ and showing overall consistency of results.
B At	A body of evidence consisting of studies rated as 2++, directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1+.
C	A body of evidence consisting of studies rated as 2+ directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 2++.
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+.

times, the development group finds important practical aspects that must be highlighted and for which no scientific evidence has been found. In general, these cases are related to some aspects of the treatment that nobody would normally question and they are evaluated as points of "good clinical practice".

√	Recommended practice based on clinical experience and the consensus of the editorial team.

Sonstige methodische Hinweise

Keine Beteiligung Betroffener

Empfehlungen:

General Management

Empfehlung 1: Patients with DM-associated rapidly progressive interstitial lung disease anti-MDA5 (+) should be treated with combination therapy as a first option. (Recommendation grade D)

Scientific evidence on efficacy and safety of the drugs used for the treatment of anti-MDA5 (+) associated RPILD comes from observational studies and case reports. All the identified studies include a combined or progressive administration of immunosuppressive drugs with or without support therapies. The usual approach comprises a combined schedule of glucocorticoids (oral prednisone or prednisolone, intravenous methylprednisolone pulse therapy, or both), immunosuppressive drugs (intravenous cyclophosphamide or calcineurin antagonists such as cyclosporine A or tacrolimus), and intravenous immunoglobulin as an adjuvant therapy [10,16-19,22,28-51] (Level of evidence 3).

Obtained data is mainly focused on mortality and prognosis factors that contribute to an interstitial pneumonia favorable outcome. In summary, all the studies gave support to the combination therapy. Accordingly, and considering their clinical expertise, the elaborating group also supports combination therapy as the best available treatment in order to improve the clinical outcome and reduce the mortality in these patients.

Combination therapy

Empfehlung 2: A combination therapy including glucocorticoids plus a calcineurin antagonist (cyclosporine A or tacrolimus), or triple therapy adding intravenous cyclophosphamide to the previous schedule, are both considered good initial alternatives. (Recommendation grade D)

Recommendation 2a: Both, cyclosporine A and tacrolimus are considered equally good therapeutic options. The choice of any of them will depend on the safety profile and patients' characteristics. (Recommendation grade ✓).

A systematic review of the scientific evidence allowed us to identify several observational studies (case series) focused on the pharmacological combination therapy in patients with DM-associated RPILD and anti-MDA5 positive antibodies.

Three retrospective studies [16,19,37] aimed to analyze the differences in clinical activity and pulmonary function parameters between patients with anti-MDA5 positive antibodies and RPILD who died or survived, and to determine the main prognostic factors. The first study [16], included 20 RPILD anti-MDA5 (+) patients, 12 of them received treatment with a combination of prednisolone and cyclophosphamide plus calcineurin antagonists (triple therapy). Seven out of 12 (58%) died and the other 5 (42%) developed a favorable outcome and survived. Eight patients received treatment with a combination of prednisolone and either cyclophosphamide or a calcineurin antagonist (2 died and 6 survived). The number of patients treated with the combination including a calcineurin antagonist is not specified.

At the second study [19] the authors identify 17 anti-MDA5 positive patients who develop RPILD among a series of 95 DM patients. In this study only one (16%) out of 6 patients who received triple therapy (prednisolone, cyclophosphamide and calcineurin antagonists) died. Among the other 11 who were treated with a combination therapy including prednisolone plus either cyclophosphamide or calcineurin antagonists, 3 (27%) died.

Finally, the third of the 3 retrospective studies previously me ntioned [37] included 12 patients diagnosed with DM anti-MDA5 positive who develop a RPILD. Eight of these patients received combination therapy with prednisolone and cyclosporine, and only 3 (25%) died. The other 4 patients received triple therapy (prednisolone, cyclophosphamide and cyclosporine), being the mortality of 75% (3 patients) (Level of evidence 3).

Other study [22] analyzed 11 patients positive to anti-MDA5 with RPILD, who were also treated with triple therapy, being tacrolimus the calcineurin inhibitor used. A good clinical response was noticed and none of the patients died, although a non-significant trend to clinical relapse was observed in those patients who received a reduced number of intravenous cyclophosphamide cycles (Level of evidence 3).

Hozumi et al [40] reported 15 patients diagnosed with DM anti-MDA5 positive and ILD, 13 of them with anti-MDA5 positive and RPILD. Ten were treated with combination therapy that included prednisolone plus a calcineurin antagonist (cyclosporine in 8 patients and tacrolimus in 2), and 5 received a triple therapy scheme (prednisolone, cyclophosphamide and cyclosporine). Six out of 15 patients died, 5 of them due to respiratory failure and the other one of unknown cause (Level of evidence 3).

Other 4 retrospective studies adding indirect evidence were identified. Patients reported in these studies were mostly but not all anti-MDA5 positive, and there was no specific information for this subgroup. Tanizawa et al. [39] included 12 anti-MDA5 positive patients, five of whom developed RPILD. Seven out of the 12 patients died, five of them with RPILD, being six of them treated with triple therapy (glucocorticoid, cyclophosphamide and cyclosporine) and the other one with the combination of glucocorticoids and cyclosporine. Ikeda et al. [34] reported 10 patients positive to anti-MDA5 who developed ILD, 6 (60%) of them died, all with the RPILD phenotype, even though they received triple therapy. Ma X et al [35], reported 7 anti-MDA5 positive patients with RPILD, being treated with triple therapy including mycophenolate, leflunomide, intravenous immunoglobulin, and some naturist therapies (i.e. Chinese herbs). Six out of 7 (85%) died. A study published by Nakashima, et al [10], compare a cohort of 14 anti-MDA5 patients who develop RPILD and were treated with triple therapy (prednisolone, cyclophosphamide and cyclosporine) with a historical cohort who received standard therapy (not described). Mortality in the group treated with triple therapy was 25% in comparison with 71.4% of the historical cohort (Level of evidence 3).

Overall, published data are scarce and the level of evidence of the studies is weak. Hence, case reports were also included in the analysis, with a total of 53 anti-MDA5 positive DM patients with RPILD. The outcome of the reported cases that were treated with combination therapy (glucocorticoids, plus either cyclophosphamide or cyclosporine, or a combination of both immunosuppressive drugs) [28-32,36,38] was good, and only 2 cases died [30,36]. Other reported cases that used tacrolimus instead of cyclosporine [33,41-43,45,46], also had a good prognosis, except for two cases [45,46] and one out of the three reported cases in the Koguchi-Yoshioka H et al study [42] (Level of evidence 3).

In summary, from the analysis of the reported cases, 21 patients (40%) died, and 32 (60%) improved after immunosuppressive therapy. Most cases received combination therapy with glucocorticoids (either oral prednisone or prednisolone or pulsed methylprednisolone), cyclophosphamide and/or a calcineurin antagonist (cyclosporine or tacrolimus). […]

Two more published cases that included from the onset mycophenolate added to the combination therapy of glucocorticoid and calcineurin antagonists were identified. One is the case number 9 from Hoa et al [17] who presented a good outcome after being treated with mycophenolate, tacrolimus and glucocorticoids, and the other one (case 9) with RPILD reported

by Takada et al. [44] developed a progressive course and died in spite of triple therapy with glucocorticoid, mycophenolate and cyclosporine (Level of evidence 3).

The expert group, therefore, considers that there is no enough information for a triple therapy recommendation including mycophenolate plus glucocorticoids and calcineurin antagonists from the disease onset. Lastly, other studies providing indirect information have been identified. They included patients diagnosed with DM and negative for or with unknown anti-MDA5 antibodies status, who developed a RPILD. Combination therapy (glucocorticoid and calcineurin antagonists from the onset) effectively reduced mortality in comparison with historical controls treated only with glucocorticoids, mainly in those patients with acute ILD (6.7% vs. 28.6%, p=0.043) and (31% vs. 68%, p=0.049) [16,19]. Moreover, those DM patients with acute or subacute ILD who received triple therapy with glucocorticoids, cyclophosphamide and cyclosporine, had a survival of 50% [40,44].

Improvement of pulmonary function parameters, creatine-kinase and manual muscle test (MMT) score and a reduction in glucocorticoid requirement with an increase in disease-free survival (HR: 0.25; CI 95% 0.010-0.66, p=0.005) [34,35] was observed when tacrolimus was added to the standard immunosuppressive therapy (prednisolone and/or cyclophosphamide and/or cyclosporine). (Level of evidence 3).

Considering these results, the expert group stated that the first therapeutic option in anti-MDA5 positive patients with RPILD is a combination therapy including glucocorticoids plus the administration of a calcineurin antagonist, or alternatively a triple therapy with glucocorticoids, calcineurin antagonists and pulses of intravenous cyclophosphamide. If cyclophosphamide is not feasible, the administration of mycophenolate may be a good option. Otherwise, although studies performed in myositis patients with RPILD, negative for or with unknown anti-MDA5 antibodies, suggest that adding tacrolimus to other immunosuppressive drugs (glucocorticoids and/or cyclophosphamide and/or cyclosporine) may improve the outcome of these patients, the evidence is so scarce that it does not allow to establish a preference for tacrolimus over cyclosporine. Although cyclosporine A has been the most commonly used calcineurin antagonist in patients with RPILD and positive anti-MDA5 antibodies, and the benefits of adding tacrolimus to other immunosuppressive drugs have not been specifically evaluated, the expert group considered that the choice of tacrolimus or cyclosporine will depend on the safety profile and the patient clinical background.

Recommendation 3: When calcineurin antagonists are not feasible, consider combination therapy with glucocorticoids and other immunosuppressive drugs such as cyclophosphamide and/or mycophenolate mofetil, or adding rituximab to any one of the previous schedules (Recommendation grade 3).

Recommendation 3a: The choice of one of these drugs will depend on the individual characteristics of the patient and the clinician experience (Recommendation grade ✓).

Double therapy with glucocorticoid and cyclophosphamide was used in several retrospective studies and case reports. Two retrospective studies previously mentioned in recommendation 216, 19 describe 19 cases (8 and 11 patients, respectively) treated with a double therapy combining glucocorticoid and cyclophosphamide or a calcineurin antagonist, 14 patients of whom survived (6 and 8, respectively). The number of patients treated with the combination including cyclophosphamide is not specified. Besides, the case reported by Goussot [32] received this double therapy and also survived (Level of evidence 3).

The evidence about the efficacy and safety of mycophenolate in the treatment of RPILD associated with anti-MDA5 is scarce and indirect, based on 12 patients from case series and

reports [47-50,52]. Mycophenolate was combined with other immunosuppressants resulting in three patients who died and nine with clinical improvement. Six out of nine patients who improved did not receive calcineurin antagonists as part of the therapeutic strategy. Two of the three patients who died received sequential treatment with several immunosuppressants, which did not include calcineurin antagonists [48,49] (Level of evidence 3).

In assessing these results, the expert panel considered that when calcineurin antagonists are not feasible, either double therapy with glucocorticoid and cyclophosphamide or mycophenolate or triple therapy with the three of them with or without intravenous immunoglobulins might also be a valid therapeutic option. Thirteen patients treated with rituximab due to RPILD associated to anti-MDA5 antibodies have been reported. Six of them did not receive calcineurin antagonists as part of the combined therapy with cyclophosphamide with or without mycophenolate [17,47-49,53]. Of these, four patients died [17,48,49] and only two improved [47,53] (Level of evidence 3).

According to these data, the expert panel considers that adding rituximab to the combination of glucocorticoid and cyclophosphamide must be taken with caution.

Therapy for the refractory patient

Recommendation 4: In patients with DM-associated rapidly progressive interstitial lung disease anti-MDA5 (+) who do not respond to combination therapy with glucocorticoids plus immunosuppressive drugs, clinicians have to consider the following alternatives: Adding one of these immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, rituximab, basiliximab or tofacitinib) to the current therapy (Recommendation grade D)

- Change one immunosuppressant for another (Recommendation grade ✓).

Although definition of a refractory patient can differ from one study to another, it is generally accepted as a lack of response after administration of the classic therapeutic schedule following recommendations 2 and 3. Some studies have defined treatment failure in these patients when they fulfill the following conditions at least 1 week after the institution of triple therapy: deteriorating respiratory symptoms; increasing alveolo-arterial O2 tension difference (AaDO2); newly-emerging or expanding GGO/consolidation on chest imaging; increasing ferritin levels, and the personal impression of clinical worsening of the patient under triple therapy by the attending physicians [54]. Evidence-based analysis identified several drugs used as rescue therapy in refractory patients with anti-MDA5 positive DM-associated RPILD. Rituximab has been added to the standard immunosuppressive therapy (recommendations 1 and 2) in patients with RPILD impairment [17,48,49,53,55-59]. Eight out of 13 reported patients died, even though rituximab had been added [17,48,49,55,59], and 5 improved [17,53,56,57], although in a single case relapse did not involve the lung [47] (Level of evidence 3).

As previously reported, recommendations 2 and 3 gather the available evidence (case reports) on the use of mycophenolate in combination with other immunosuppressive drugs. Only a single patient refractory to the initial triple therapy that finally improved after adding mycophenolate has been identified [50] (Level of evidence 3).

A single study highlighted the efficacy of basiliximab (an anti-CD25/sIL-2R monoclonal antibody) [60]. It included 4 patients who were refractory to immunosuppressive therapy including prednisone, cyclosporine, and intravenous immunoglobulin. Basiliximab showed efficacy in 3 of the 4 patients [60] (Level of evidence 3)

Another option in the case of failure to the conventional triple therapy is to replace one immunosuppressant for another. Nevertheless, in the case of calcineurin antagonists, Yoshida et al [46] described the case of a patient refractory to triple immunosuppressive therapy who died despite switching cyclosporine by tacrolimus (Level of evidence 3).

Finally, two studies have found a good response adding the Janus kinase inhibitor tofacitinib to conventional triple therapy in six refractory cases. Kurasawa et al. [54] reported a survival rate of 60% in tofacitinib-treated patients (three out of five) compared to none out of six historical controls with similar poor-prognostic factors. However, 80% of tofacitinib-treated patients presented varicella-zoster virus reactivation and 100% developed cytomegalovirus infection. Kato et al. [61] reported a case of refractory ILD with pneumomediastinum responsive to tofacitinib add-on therapy (Level of evidence 3).

Considering these results, the expert group suggests that in refractory cases to standard triple immunosuppressive therapy (recommendations 2 and 3), adding to a new immunosuppressant or switching one for another may be considered valid therapeutic alternatives.

Recommendation 7: Lung transplantation should be considered as a therapeutic option in patients with refractory RPILD associated with anti-MDA5. Early referral for transplant eligibility assessment is recommended at the time of ILD diagnosis (Recommendation grade ✓).

In patients with interstitial lung disease associated with connective tissue disease (CTD), lung transplantation is contraindicated at many centers because of the impact of pre-existing conditions on post-transplant outcomes. Potential contributors to poor outcomes include gastroesophageal reflux (thought to cause bronchiolitis obliterans syndrome), renal disease (as it complicates management of immunosuppressive and antimicrobial agents commonly used after transplantation), and extra-pulmonary disease such as myositis (which complicates management of immunosuppression and rehabilitation after transplantation and the risk of malignancy association). In fact, less than 1% of all lung transplants worldwide between 1995 and 2015 were given to patients with CTD associated with lung disease [75]. However, recent studies suggest that post-transplant outcomes in these patients do not differ significantly from those in patients with non-CTD [76-78] which supports CTD patients to be considered as part of lung transplant candidates [79]. Data on lung transplantation in anti-MDA5 positive DM associated RPILD are scarce and limited to case series and reports. Selva-O'Callaghan et al. [80] reported two cases of unsuccessful lung transplantation in patients with DM-associated RPILD complicated with pneumomediastinum, subcutaneous emphysema and acute alveolar injury. Several years later, stored serum samples of these patients, which were obtained at the beginning of the disease, were analyzed. They turned out to be positive for anti-MDA 5 antibodies (author personal communication). On the other hand, Shoji et al. [81] reported a case of bilateral living-donor lobar lung transplantation with uneventful postoperative course, who also was able to perform daily activities without oxygen seven months after surgery. Besides, a patient reported by Leclair et al. [72], who underwent bilateral lung transplantation after prolonged VV-ECMO, was able to resume his normal life with a survival period to date of twelve years in remission. More recently, a patient reported by Deitchman et al. [73] and three out of eight anti-MDA5 positive RPILD refractory patients reported by Huang et al. [74] survived after lung transplant being previously supported by VV-ECMO. (Level of evidence 3).

Therefore, the expert panel strongly recommends referring soon patients with ILD associated with anti-MDA5 antibodies to centers with experience in the evaluation and management of lung transplantation in CTD.

Other treatment options

Recommendation 8: Azathioprine, methotrexate and leflunomide are not recommended as an induction therapy in RPILD associated with anti-MDA5 antibodies (Recommendation grade ✓).

The evidence about the efficacy and safety of azathioprine in RPILD associated with anti-MDA5 is scarce with uneven results in the only five reported cases. With respect to this, two patients received azathioprine as part of sequential therapy with non-calcineurin antagonists immunosuppressants (cyclophosphamide, mycophenolate and rituximab) but they did not survive [48,49]. However, case 5 of the Hoa series [17] who developed pleural effusion, improved after adding azathioprine to glucocorticoid and tacrolimus double therapy. Finally, azathioprine monotherapy plus glucocorticoid resulted in ILD improvement in one case [82] and fatal outcome in another [83] (Level of evidence 3).

Information about the use of methotrexate in anti-MDA5-associated ILD has only been retrieved from seven patients with the non-RP form. In all of them, methotrexate was used as part of the combined treatment with other immunosuppressants (mycophenolate, hydroxychloroquine, azathioprine, or rituximab). All patients presented a good clinical course without progression of the pulmonary involvement [8,84]. Both, the scarce number of patients and the association with other immunosuppressants make difficult to evaluate the real effect of methotrexate in the observed outcome (Level of evidence 3).

Leflunomide has only been evaluated in seven patients with anti-MDA5-associated RPILD [35]. It was used in combination with Chinese herbs and other immunosuppressants, including glucocorticoid, cyclophosphamide, calcineurin antagonists, mycophenolate and intravenous immunoglobulins, thus being very difficult to evaluate, in this context, the role of this drug in the fatal outcome of 6 out of the 7 patients (85%) (Level of evidence 3).

Considering the results of all these studies and the scarce clinical experience, the elaborating group considered that azathioprine, methotrexate and leflunomide should not be recommended in the management of RPILD, particularly as an induction therapy.

Recommendation 9: Infliximab is not recommended in anti-MDA-5 associated RPILD treatment (Recommendation grade ✓).

Regarding the use of infliximab in inflammatory myopathy-associated RPILD, only a retrospective case series of fourteen non-MDA5 treated patients in combination with conventional immunosuppressant therapy has been identified [9]. Ten of them had the amyopathic clinical form. All the fourteen patients were initially treated with methylprednisolone combined with cyclophosphamide in seven, mycophenolate in one, tacrolimus in three, cyclosporine in one, methotrexate in another one and immunoglobulins in five. Also, all of them received infliximab at a dose of 5 mg/kg/i.v. at week 0, 2, 6 and then every eight weeks. The ten patients (71%) treated in the early phase did have a favorable response while the other four (29%) who received infliximab after the respiratory failure, died (Level of evidence 3).

Despite this data, the expert panel has considered the clinical evidence showing that anti-TNF agents may cause serious ILD and, therefore, cannot recommend infliximab use in the therapeutic management of these ILD's patients.

Recommendation 10: Although pirfenidone has been added to conventional immunosuppressant treatment in DM-associated subacute interstitial pneumonia with

pulmonary fibrosis, the expert panel may not recommend its use in patients with RPILD associated to anti-MDA5 antibodies (Recommendation grade ✓).

Data on the use of antifibrotic agents comes from a prospective study [52] that included 30 patients with CADM-associated RPILD treated with pirfenidone in addition to conventional immunosuppressive treatment (glucocorticoids, cyclosporine and mycophenolate) compared with a historical cohort of 27 patients treated with conventional therapy. Twenty-two of 30 patients from the pirfenidonetreated group were anti-MDA5 positive versus 4 of 27 patients of the control group. Overall, mortality in the pirfenidone-treated group was lower although did not reach statistical significance compared with the control group (36.7% vs. 51.9%, p=0.223). An analysis of the subgroup of patients with acute ILD (<3month) (n=30) disclosed identical mortality for case and control groups (50% vs. 50%, respectively; p=0.386). However, in patients with subacute ILD (3 to 6 month) (n=19), the mortality in pirfenidone-treated patients was lower than that of the control group (90% vs. 44%, p=0.045). A subgroup analysis describing only anti-MDA-5 patients was not performed. No serious adverse events were described (Level of evidence 3).

Zusammenfassung Therapieempfehlungen:

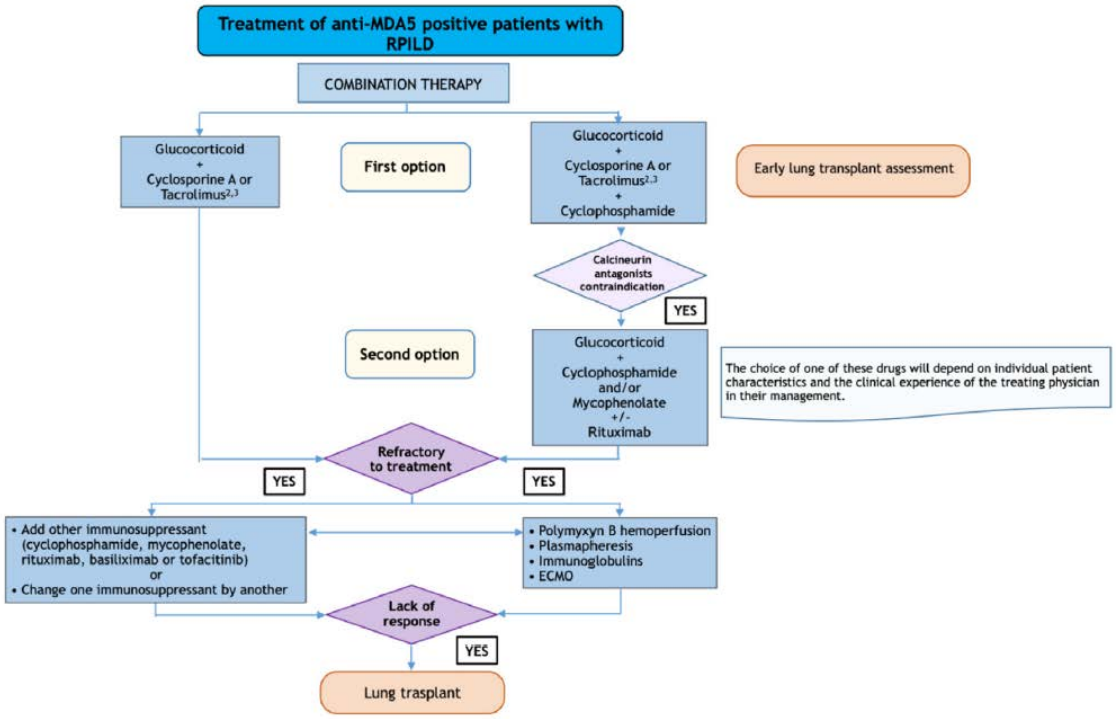

Fig. 2. Treatment of RPILD in patients with anti MDA5 antibodies.

Referenzen aus Leitlinien

Siehe Anhang 1

Price E et al., 2017 [3].

British Society for rheumatology

The British Society for Rheumatology guideline for the management of adults with primary Sjögren´s Syndrome

Zielsetzung/Fragestellung

This document aims to provide a pragmatic, practical guideline for the management of adults with pSS (Primary Sjogren's Syndrome).

Methodik

Grundlage der Leitlinie

- Gremium unterschiedlicher medizinischer Disziplinen
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: Any conflicts of interest among members of the working party were fully declared.
- Systematische Suche, Auswahl und Bewertung der Evidenz: Identified papers were reviewed, categorized and the level of evidence graded according to international criteria from Ia through to IV and A through to B
- Formale Konsensusprozesse und internes Begutachtungsverfahren dargelegt: The wording and content of the recommendations were subjected to a formal Delphi process using online surveys to determine the eventual strength of agreement (SOA) for each recommendation
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Unklar, ob regelmäßige Überprüfung der Aktualität vorgenommen wird

Recherche/Suchzeitraum:

- all relevant evidence in the Cochrane Library, MEDLINE (Ovid and PubMed) and EMBASE from 1990 to current (February 2015 and updated September 2015).
- Additional references were added through regular updates to the draft recommendations up to January 2016. Non-English language papers were excluded unless a translation was published.

LoE, GoR

Level of evidence	
Ia	From meta-analysis of RCTs
Ib	From at least one RCT
IIa	From at least one controlled study without randomization
IIb	From at least one type of quasi-experimental study
III	From descriptive studies such as comparative studies, correlation studies of case-control studies
IV	From expert committee reports or opinions and/or clinical experience of respected authorities
Determination of recommendation strength	
A	Category 1 evidence

B	Category 2 evidence or extrapolated recommendations from category 1 evidence
C	Category 3 evidence or extrapolated recommendations from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendations from category 2 or 3 evidence

Sonstige methodische Hinweise

- Auswahl und Zusammensetzung der Leitlinen-Gruppe nicht beschrieben
- Keine Beteiligung Betroffener
- Kein externes Begutachtungsverfahren
- Formale Qualitätsbewertung der Evidenz ist nicht beschrieben.
- Unklar, ob regelmäßige Überprüfung der Aktualität vorgenommen wird

Unterüberschrift

Empfehlung 1:

Systemic pulmonary manifestations of Sjogren's include ILD and cysts. Usual interstitial pneumonitis and non-specific interstitial pneumonitis are the most commonly reported. In general systemic steroids are recommended as first line treatment, then subsequently various immunosuppressives, including CYC and AZA, rituximab and anti-malarials depending on steroid responsiveness [127-129].

Empfehlung 2: AZA is not routinely recommended for management of uncomplicated Sjo¨ gren's but may be considered in patients with systemic complications, for example, lung disease, myelopathy and cytopaenias. Level of evidence III/C; SOA 9.09 (100%).

AZA (azathioprine) has been reported as helpful in case reports for systemic complications such as lung disease [150], myelopathy [151] and cytopaenias [152], but a double blind placebo controlled trial in a small cohort of patients with uncomplicated disease suggested that it did not have a routine role in treatment and was associated with a high frequency of side effects [153]. There is, however, some evidence for efficacy of AZA in both usual interstitial pneumonitis and non-specific interstitial pneumonitis, the most commonly reported forms of ILD in Sjögren's [128, 129, 154, 155]. Discontinuation rates of AZA due to non-respiratory side effects may be higher than for mycophenolate although efficacy is similar in patients with ILD [156].

Empfehlung 3: The use of mycophenolate may be considered in patients with systemic complications such as cytopaenias or lung disease. Level of evidence III/C; SOA 9.1 (100%).

A single centre, open-label pilot trial of mycophenolate in 11 patients reported subjective improvement of ocular dryness and reduction in artificial tear use, but objective evidence of significant glandular improvement in only two patients with short disease duration. There was significant reduction in hypergammaglobulinaemia and RF levels and increase in complements and white cell levels [161]. A case report [162] documents successful treatment of refractory agranulocytosis with mycophenolate in a patient with primary Sjögren's. There is emerging evidence supporting the use of mycophenolate in patients with CTD related ILD including SS [163, 164]. Mycophenolate has been show to stabilize scleroderma associated ILD in a randomized controlled trial [165]. There are to date no similarly robust clinical trials supporting

mycophenolate in Sjögren's associated ILD, but there are anecodatal reports and small case series suggesting benefit [166, 167].

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, June 2020) am 26.06.2020

#	Suchfrage
1	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees
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* NEAR/3 pulmon*):ti,ab,kw
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	MeSH descriptor: [Scleroderma, Systemic] explode all trees
12	(systemic NEXT (scleroderma* OR scleros*)):ti,ab,kw
13	MeSH descriptor: [Dermatomyositis] explode all trees
14	(dermatomyosit* OR polymyosit*):ti,ab,kw
15	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
16	(rheumatoid NEAR/3 arthrit*):ti,ab,kw
17	MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees
18	(lupus NEAR/3 erythematosus):ti,ab,kw
19	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20	(lung OR pulmon* OR pneumon*):ti,ab,kw
21	#19 AND #20
22	#10 OR #21
23	#22 with Cochrane Library publication date from June 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 26.06.2020

#	Suchfrage
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] AND disease*[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] AND pulmon*[tiab]
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	(#10) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
12	((#11) AND ("2015/06/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 26.06.2020

#	**Suchfrage**
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] AND disease*[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] AND pulmon*[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 erythematosus[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*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
24	(#23) AND ("2015/06/01"[PDAT] : "3000"[PDAT])
25	(#24) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Abbildung 1: Referenzen aus Romero-Bueno F et al. [4]…

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Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei der Behandlung „einer interstitiellen Lungenerkrankung bei Erwachsenen mit systemischer Sklerose (SSc-ILD)**“ und „**for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype (inoffizielle Übersetzung: zur Behandlung chronisch fibrosierender interstitieller Lungenerkrankungen bei Erwachsenen mit progressivem Phänotyp“. **„Wie sieht die Versorgungspraxis in Deutschland aus?**

1. Sklerodermie-assoziierte interstitielle Lungenerkrankung (SSc-ILD)

Die systemische Sklerose (SSc) ist eine Bindegewebserkrankung (Kollagenose), deren Ätiologie bisher nicht aufgeklärt wurde. Es wird jedoch ein Zusammenspiel aus genetischer Prädisposition und Umweltfaktoren als Ursache vermutet (1). Pathogenetisch beruht die SSc auf (auto)immunologisch-entzündlichen Mechanismen, die neben dem namensgebenden Hautbefall auch Gefäße (Vaskulopathie) und innere Organen erfassen. In einem hohen Prozentsatz (ca. 80 %) entwickeln SSc Patienten auch eine Lungenbeteiligung im Sinne einer interstitiellen Lungenerkrankung (SSc-ILD), die mehrheitlich (ca. 80 %) dem Muster einer nicht-spezifischen interstitiellen Pneumonie (NSIP) entsprechen, seltener treten davon abweichende Muster wie die Usual Interstitial Pneumonie (UIP Muster, „gewöhnliche Lungenfibrose“) oder organisierende Pneumonie (OP) auf (1). Die Lungenbeteiligung bei SSc-ILD ist Prognose-limitierend und stellt die häufigste Todesursache von SSc Patienten dar (2). In Placebo kontrollierten prospektiven Studien konnte gezeigt werden, dass sowohl eine immunmodulatorische Therapie mit Cyclophosphamid (CYC) als auch alternativ mit Mycophenolatmofetil (MMF) das Fortschreiten der Lungenbeteiligung gemessen an der Abnahme der forcierten Vitalkapazität (FVC) in der Lungenfunktion signifikant abmildert bzw. im Verlauf von 24 Monaten sogar zu einer leichten Zunahme der FVC führt (3-5). Diese Studien werden als „proof of concept“ dafür gewertet, dass eine immunmodulatorische (immunsuppressive) Therapie bei Sklerodermiepatienten mit Lungenbeteiligung für diese einen Vorteil darstellt, so dass heute

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verschiedene immunmodulatorische Therapien, oft auch mit Prednisolon und Kombinationen verschiedener Immunsuppressiva eingesetzt werden, wobei ein einheitlicher Behandlungsstandard nicht existiert (6). Keine der genannten Therapien ist allerdings in Deutschland für diese Indikation zugelassen, nur für systemische Glukokortikosteroide (GKS) besteht eine allgemeine Zulassung für eine Alveolitis im Allgemeinen und eine Lungenfibrose im allgemeinen, wobei höhere Dosierungen die Gefahr einer renalen Krise bei Sklerodermiepatienten erhöhen und GKS z.B. bei der idiopathischen Lungenfibrose zur Dauertherapie kontraindiziert sind. Die Indikationsstellung für eine solche immunmodulatorische Therapie, die ja durchaus auch Nebenwirkungen haben kann, orientiert sich an der Schwere der Lungenbeteiligung und der beobachteten Krankheits- und Entzündungsaktivität, wobei die Publikation von Goh et al. eine Orientierung bietet (7).

Nachdem eine zunehmende Fibrose des Lungenparenchyms durch die alleinige immunmodulatorische Therapie nicht verhindert wird, wurde in einer aktuellen Studie das antifibrotisch und anti-inflammatorisch wirkende Medikament Nintedanib, für das eine Zulassung für die Indikation idiopathische Lungenfibrose (IPF) in Deutschland existiert, für die Indikation SSc-ILD getestet (SENSCIS-Studie). In der Placebo kontrollierten, randomisierten, prospektiven Studie wurden SSc-ILD Patienten über ein Jahr behandelt (8). Eingeschlossen wurden erwachsene Patienten mit einem Krankheitsverlauf von maximal 7 Jahren und Befall von mindestens 10 % des Lungenparenchyms im HRCT sowie einer FVC > 40 % des Sollwertes und einer Diffusionskapazität zwischen 30 und 89 % des Sollwertes. Eine stabile immunmodulatorische Therapie mit Prednisolon bis 10 mg/die, Mykophenolatmofetil oder Methotrexat war als Comedikation erlaubt aber nicht notwendig (8). In dieser Studie zeigte sich ein signifikanter Effekt von Nintedanib auf die Krankheitsprogression gemessen als Abfall der FVC nach einem Jahr (8). Basierend auf dieser Studie erhielt Nintedanib im Mai 2020 die Zulassung für die Behandlung von SSc-ILD Patienten.

Ein Nebenaspekt der SENSCIS-Studie war die Beobachtung, dass etwa die Hälfte der Patienten bei Studieneinschluss unter einer stabilen immunmodulatorischen Therapie mit Mykophenolatmofetil stand, während die andere Hälfte zum Zeitpunkt des Einschlusses in die Studie bzw bis zu 6 Monate zuvor ohne Therapie war (8). In der Placebogruppe der SENSCIS Studie erhielten somit etwa die Hälfte der Patienten keine Therapie während die andere Hälfte Mykophenolatmofetil (bzw MTX) einnahmen. In diesem – nicht randomisierten - Vergleich bestätigte sich die Beobachtung aus der Scleroderma Lung Study II, wonach Mykophenolatmofetil den Verlauf der FVC günstig beeinflusst und zwar auch zusätzlich zu Nintedanib (5,8).

Aktuell besteht in Deutschland somit hinsichtlich der zugelassenen Therapie für SSc-ILD die paradoxe

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Situation, dass für die weit verbreitete und nach Studienlage auch wirksame immunmodulatorische Therapie der SSc-ILD insbesondere mit Mykophenolatmofetil, welches insbesondere bezüglich der Nebenwirkungen erhebliche Vorteile gegenüber Cyclophosphamid und Azathioprin aufweist, keine Zulassung besteht und nur die „off label“ Anwendung möglich ist, während das neue Medikament Nintedanib, welches auf Basis der Studiendaten sicher und wirksam ist, ein Zulassung erhalten hat und somit de facto den Therapiestandard darstellt.

Aus Expertensicht gibt es sicherlich Patienten, die mit einer Therapie mit Nintedanib von Beginn an gut behandelt sind. Es gibt aber auch Patienten, für die das Fehlen, nicht Beginnen oder Absetzen einer immunmodulatorischen Therapie ungünstige Folgen auf den Krankheitsverlauf hätte. Wünschenswert wäre es, wenn der im Bereich der SSc-ILD erfahrene Arzt die Entscheidungsfreiheit hätte, welche Therapie oder Kombination er bei welchem Patienten unter Berücksichtigung des aktuellen Krankheitsgeschehens einsetzt.

Zusammenfassend ist eine Therapie der SSc-ILD im Kontext des gesamten klinischen Bildes der Erkrankung zu sehen und interdisziplinär zu diskutieren. Eine immunmodulatorische Therapie, vorzugsweise mit MMF scheint bei hoher Entzündungsaktivität die vorzuziehende Primärtherapie darzustellen, bei ausgeprägter Fibrosierung ist auch initial bereits eine antifibrotische Therapie sinnvoll, ggf. auch in Kombination mit MMF. Eine antifibrotische Therapie bei relevanter Fibrose bzw Progress unter Immunmodulation wird aus Expertensicht als wichtiger Therapiebaustein angesehen.

2. Progressiv fibrosierende interstitielle Lungenerkrankungen (PF-ILD)

Interstitielle Lungenerkrankungen (Interstitial Lung Diseases, ILDs) sind eine ätiologisch heterogene Gruppe von Erkrankungen, die ein breites Spektrum an Differentialdiagnosen umfasst und denen gemeinsam ist, dass sich der Krankheitsprozess im „Zwischengewebe“ (Interstitium) der peripheren bronchioloalveolären Strukturen des Lungenparenchyms abspielt, welches als zartes Bindegewebe zwischen den Alveolardeckzellen und den Endothelzellen der Blutkapillaren die Struktur der Lunge bildet (9). ILDs kommen sowohl als eigenständige Krankheitsbilder (z.B. als Idiopathische Nicht-Spezifische Interstitielle Pneumonie (iNSIP), als chronische exogen-allergische Alveolitis (chronische EAA oder synonym (v.a. im angelsächsischen Schrifttum): chronic Hypersensitivity Pneumonitis cHP) oder Cryptogen Organisierende Pneumonie (COP)) vor, als auch im Kontext von Systemerkrankungen, den sogenannten Kollagenosen (=rheumatische Erkrankungen wie rheumatoide Arthritis, Sjögren Syndrom

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aber auch Sklerodermie, systemischer Lupus erythematodes, Antisynthetasesyndrome etc.) oder (selten) bei der Sarkoidose (9-11). Bei einem Teil dieser Erkrankungen besteht eine entzündliche Charakteristik, die als immunologisch oder autoimmunologisch getriggert interpretiert wird und die auf immunsuppressive Therapie anspricht. Ein Teil der Patienten entwickelt trotz Therapie aber einen progressiv fibrosierenden Phänotyp bei dem ein bindegewebiger Umbau und Vernarbung der Alveolen dominiert, der nicht bzw. nicht mehr durch immunsuppressive Therapiestrategien beeinflussbar ist (12-14). Dieser bindegewebige Umbau des Lungenparenchyms geht mit einer progressiven Abnahme der Lungenvolumina und Verschlechterung des Gasaustausches in der Lungenfunktion einher und zeigt sich in der hoch auflösenden Computertomographie (High-resolution CT, HRCT) der Lunge durch Schrumpfung der Lungenlappen, Auftreten sogenannter Traktionsbronchiektasen und Bronchiolektasen und in einem Teil der Fälle bilden sich typische Honigwaben aus. Es handelt sich dabei um CT-morphologische Charakteristika, die man typischerweise auch bei der idiopathischen Lungenfibrose (idiopathische pulmonale Fibrose, IPF) nachweisen kann und die in der aktuellen Diagnose Leitlinie der IPF beschrieben sind (15). Auf Basis dieser Beobachtungen und experimenteller Befunde lässt sich feststellen, dass diejenigen Pathomechanismen, die bei der IPF bedeutsam sind auch für die Entstehung des progressiv fibrosierenden Phänotyps der anderen, oben genannten ILDs, einschließlich der Sklerodermie-assoziierten ILD eine wichtige Rolle spielen. Die Prognose dieses progressiv fibrosierenden Phänotyps der ILDs ist ungünstig und vergleichbar mit der IPF.

Bezüglich des Behandlungsstandards ist für die ILDs insgesamt festzustellen, dass es keine spezielle, zugelassene Therapie gibt, wenn man von systemischen Glukokortikosteroiden (GKS) absieht, für die eine Zulassung für die Alveolitis und die Lungenfibrose vorliegt (z.B. für Prednisolon). In Deutschland werden ILDs daher in der Regel mit Prednisolon (oder analoge GKS) behandelt. Wenn GKS als Monotherapie nicht ausreichen oder wenn bei Dosisreduktion der GKS eine Reaktivierung der ILD auftritt werden in Anlehnung an rheumatologische und spezielle an die SSc-ILD (s.o.) kombinierte immunsuppessive Behandlungen durchgeführt wobei Azathioprin, Mykophenolatmofetil, Methotrexat, Cyclophosphamid oder auch Rituximab eingesetzt werden. Alle diese Therapien sind mit Ausnahme der GKS de facto „off label“ für ILDs. Bei weiterer Progression der Erkrankung trotz immunsuppressiver Therapie, also im Sinne eines progressiv fibrosierenden Phänotyps, steht aktuell nur für die Systemische Sklerodermie (SSc) mit ILD das Medikament Nintedanib zu Verfügung, für welches seit Mai 2020 eine Zulassung für diese Indikation besteht. Für alle anderen Indikationen bleibt der „off-label use“ der für die IPF zugelassenen Medikamente Nintedanib und Pirfenidon oder der Einschluss in klinische Studien. In einem (kleinen) Teil der Fälle besteht die Möglichkeit einer Lungentransplantation.

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Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „einer interstitiellen Lungenerkrankung bei Erwachsenen mit systemischer Sklerose (SSc-ILD)**“ und „**other chronic fibrosing interstitial lung diseases with a progressive phenotype (inoffizielle Übersetzung: zur Behandlung chronisch fibrosierender interstitieller Lungenerkrankungen bei Erwachsenen mit progressivem Phänotyp)“. **die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Kriterien für eine unterschiedliche Behandlung von SSc-ILD und progressiv fibrosierenden Krankheitsverläufen bei anderen ILDs gibt es nicht. Das zu Grunde liegende Krankeitsgeschehen wird als artverwand angesehen, wobei wie oben geschildert für den progressiv fibrosierenden Phänotyp ähnliche Pathomechanismen wie bei der IPF zu Grunde liegen. Es ist daher naheliegend, dass auch bei diesen Erkrankungen antifibrotische Medikamente wirksam sind, die auch bei der IPF Wirksamkeit gezeigt haben und zugelassen wurden. Dem entsprechend wurde auch für Patienten mit progressiv fibrosierenden ILDs, die aber sicher keine IPF und nur in wenigen Fällen eine SSc-ILD hatten, in entsprechenden Studien die Wirksamkeit von Nintedanib (16, 17) und Pirfenidon (18, Ergebnisse liegen bisher nur als Abstract vor 19) gezeigt. Eine weitere Studie konnte auch bei unklassifizierbaren progressiv fibrosierenden ILDs eine Wirksamkeit von Pirfenidon belegen (20). Somit bestätigt sich, dass es bei den ILDs eine progressiv fibrosierende Verlaufsform (d.h. einen progressiv fibrosierenden Phänotyp) gibt, der analog wie die IPF zu beurteilen ist und der dem entsprechend nach Studienlage auf die für die IPF zugelassenen antifibrotischen Medikamente Nintedanib und Pirfenidon positiv anspricht. Eine Unterscheidung unterschiedlicher Grunderkrankungen ist demgegenüber für die Therapieentscheidung nicht ausschlaggebend.Bitte begründen Sie Ihre Ausführungen.

(hier ergänzen – sofern verfügbar – auf welcher (Daten-)Grundlage basiert die Einschätzung; ggf. beifügen der zitierten Quellen)

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