

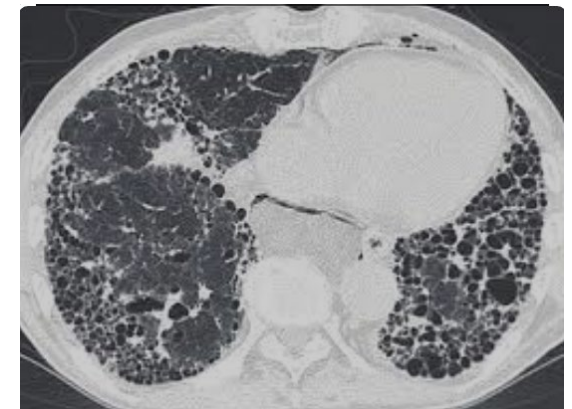
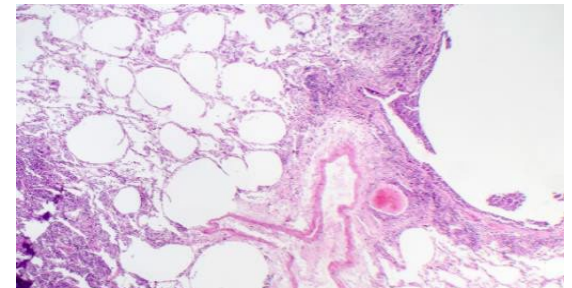
Interstitielle Lungenerkrankung bei Kollagenose: was ist neu?

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Leitende Ärztin Rheumatologie

Universitätsspital Zürich, Universität Zürich

Rheuma Workshop 9.01.2025



Conflicts of interest (last three years)

Consultancy relationship and/or research funding and/or speaker fees from:

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Interstitielle Lungenerkrankungen und Rheuma

1. Systemic autoimmune rheumatic disease (SARD)-ILDs overview
2. Screening and monitoring of SARD-ILD
3. Treatment of SARD-ILD
4. Role of the general internal medicine specialist in the care of SARD-ILD

Interstitielle Lungenerkrankungen und Rheuma

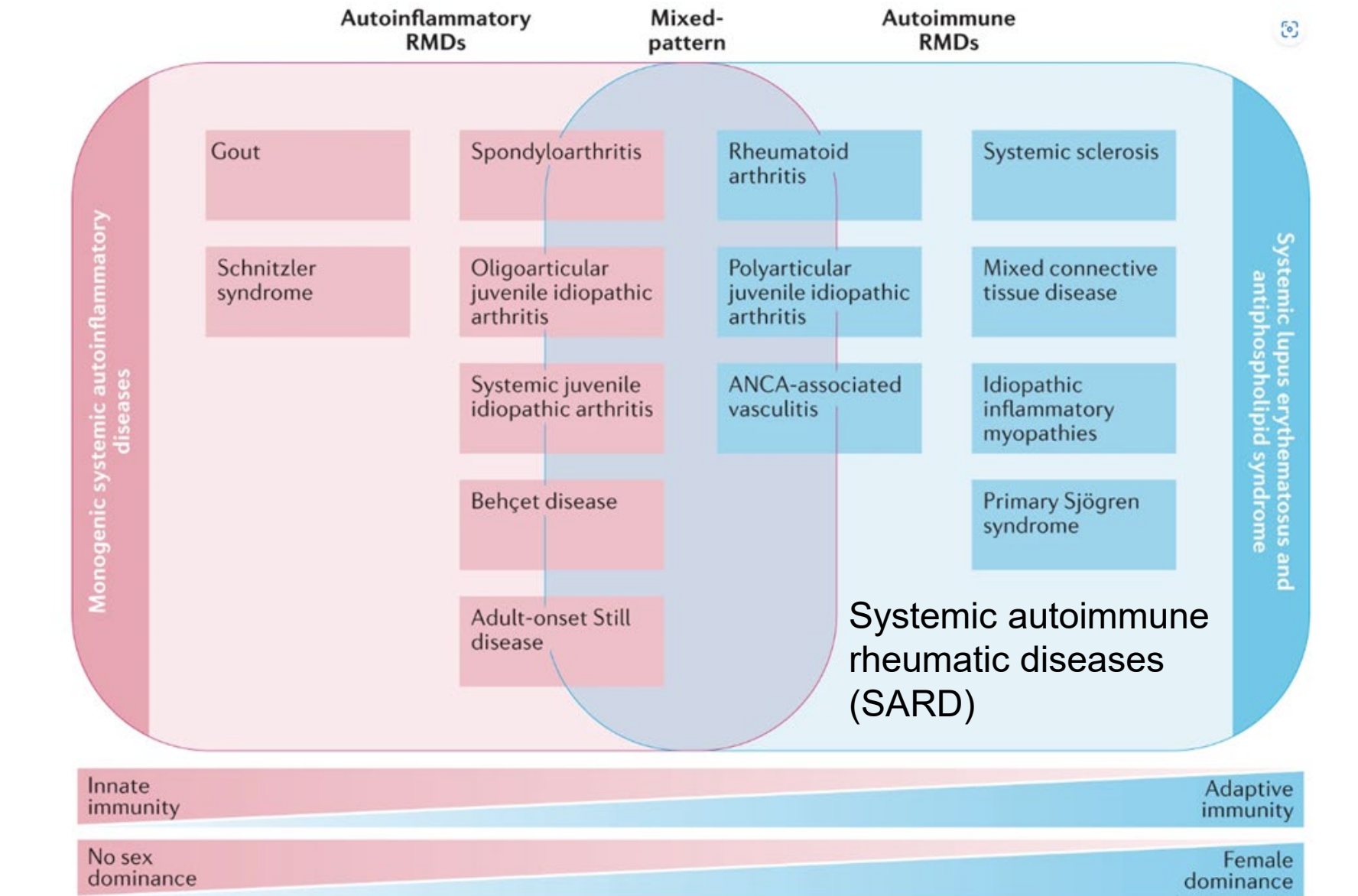
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Interstitielle Lungenerkrankungen und Rheuma

Szekanecz Z. et al.

Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases.

Nat Rev Rheumatol. 2021; 17(10):585-595.



Pulmonary manifestations in SARDs

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	-	-	+++	-
Rheumatoid arthritis	++	++	++	+	-
Primary Sjögren's syndrome	++	++	+	+	-
Mixed CTD	++	+	+	++	-
Polymyositis/ dermatomyositis	+++	-	-	+	-
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (-=no prevalence; +=low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.

Table 1: CTDs and common pulmonary manifestations

Lung and rheumatoid arthritis

1. Pulmonary noduli

- Caplan-Syndrom

2. Interstitial lung disease (RA-ILD)

3. Bronchiolitis obliterans

- bad prognosis

4. Rheumatoid pleural effusion

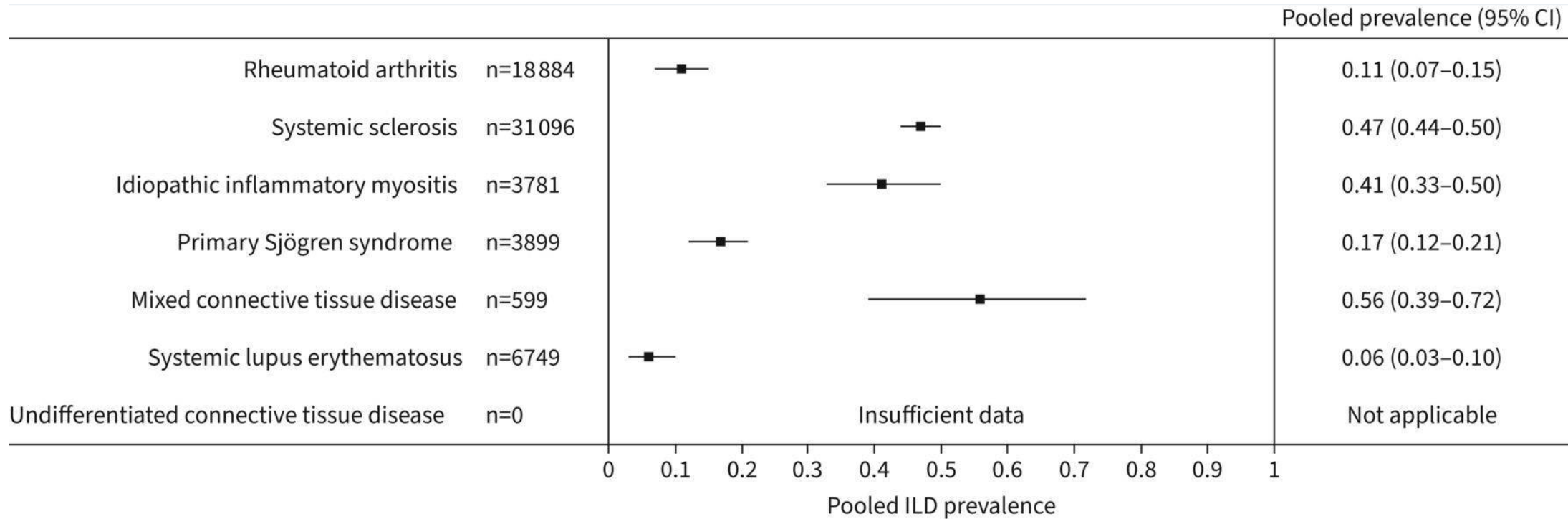
5. Pulmonary arterial hypertension

6. Infection

7. Iatrogenic: methotrexate



Interstitial lung disease (ILD) associated with SARD



Joy GM et al. Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis. *Eur Respir Rev.* 2023 Mar 8;32(167):220210

SARD-ILD: why do they matter?

High morbidity and mortality:

- Acute exacerbations: alveolar hemorrhage (e.g. in vasculitis, myositis, SLE)
 - abrupt onset, severe course, high mortality
 - Progressive pulmonary fibrosis (PPF)*: ca. 20-30% of SARD-ILD cases
 - decline in FVC of $\geq 10\%$
 - or any 2 out of the following 3:
 - decline in FVC of 5% to $< 10\%$
 - worsening of respiratory symptoms
 - increased fibrosis HRCT
- all within 24 months

RA-ILD

Prevalence: ca. 10% of RA-cases

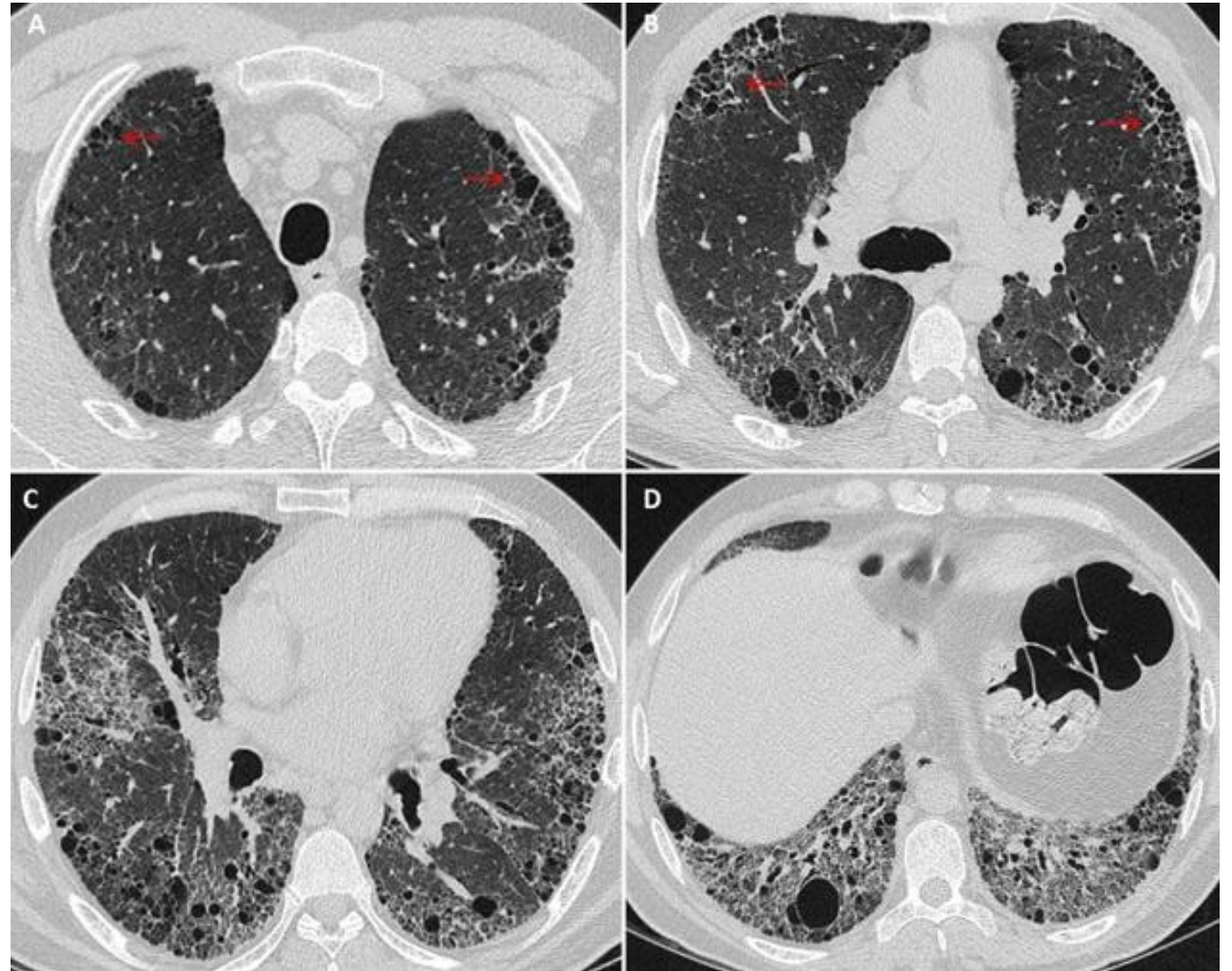
Symptoms: dyspnoea, cough

Risk factors:

- seropositive RA
- age
- male sex
- smoking

HRCT pattern:

- Usual interstitial pneumonia (UIP)
- Nonspecific interstitial pneumonia (NSIP)
- Other (organizing, lymphocytic, desquamative acute)
- Combinations of 2 or more patterns



Methotrexate is not a notable cause of RA-ILD!

Table 1 Studies in 2020 on methotrexate use and ILD presence and progression

From: [New insights into the treatment of CTD-ILD](#)

Study	Study design	Patients (patient number)	Primary findings
Juge et al. ¹	Retrospective: case-control with validation cohort	Patients with RA-ILD ($n = 410$) or with RA without ILD ($n = 673$)	Methotrexate use was associated with a reduced prevalence and delayed onset of RA-ILD
Robles- Pérez et al. ⁵	Prospective cohort	Patients with RA ($n = 40$)	Methotrexate use was not associated with the onset or progression of ILD
Ibfeft et al. ⁶	Retrospective cohort (Danish national registry)	Patients with RA ($n = 30,512$)	Methotrexate use was not associated with an increased risk of ILD
Li et al. ⁷	Retrospective cohort	Patients with RA without ILD at diagnosis ($n = 923$)	Methotrexate use was not associated with the onset or progression of ILD

Wells, A.U. *Nat Rev Rheumatol* 2021: 17, 79–80

SSc-ILD

Prevalence: 40-50%

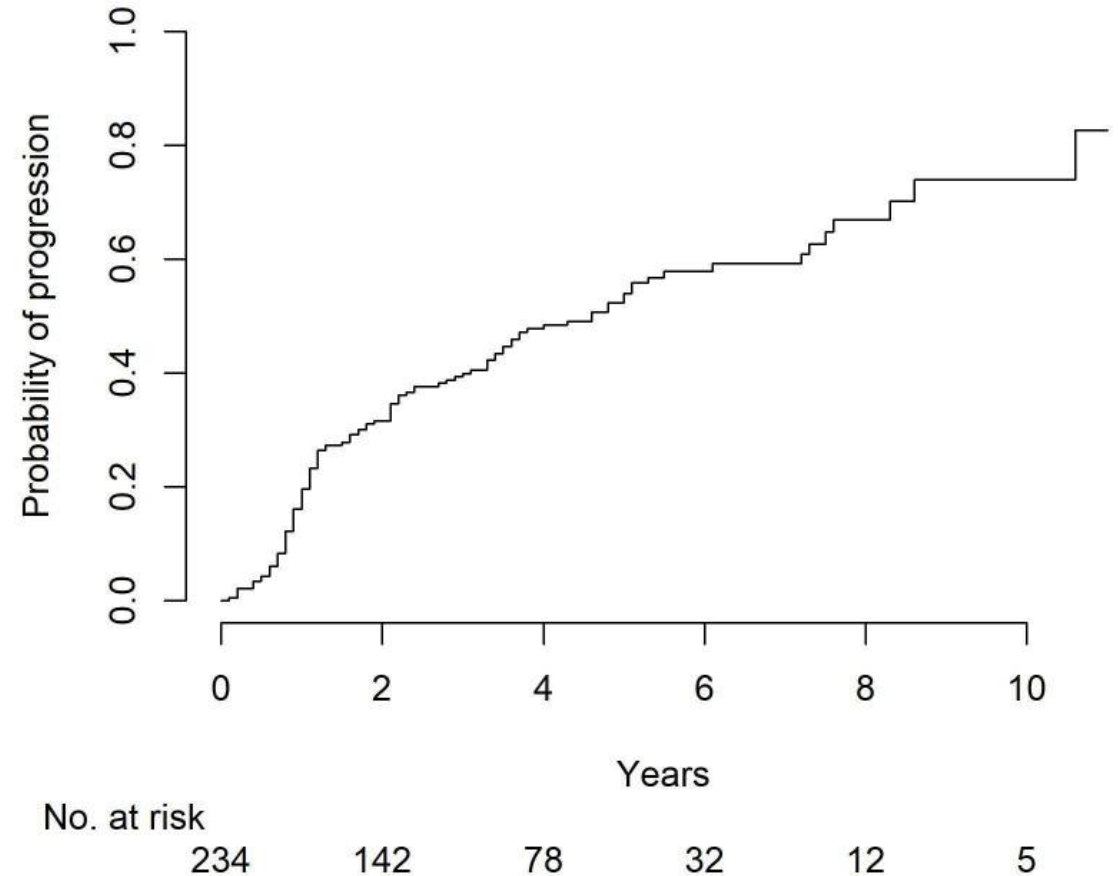
Leading cause of SSc-associated death

Risk factors:

- male sex. smoking
- Scl70-positive
- diffuse cutaneous involvement

HRCT: NSIP >UIP

Course: mostly chronic, PPF in ca. 50%



Distler O et al. Eur Respir J 2020; 55: 1902026

Milder SSc-ILD with preserved lung function contributes to respiratory-caused mortality in SSc

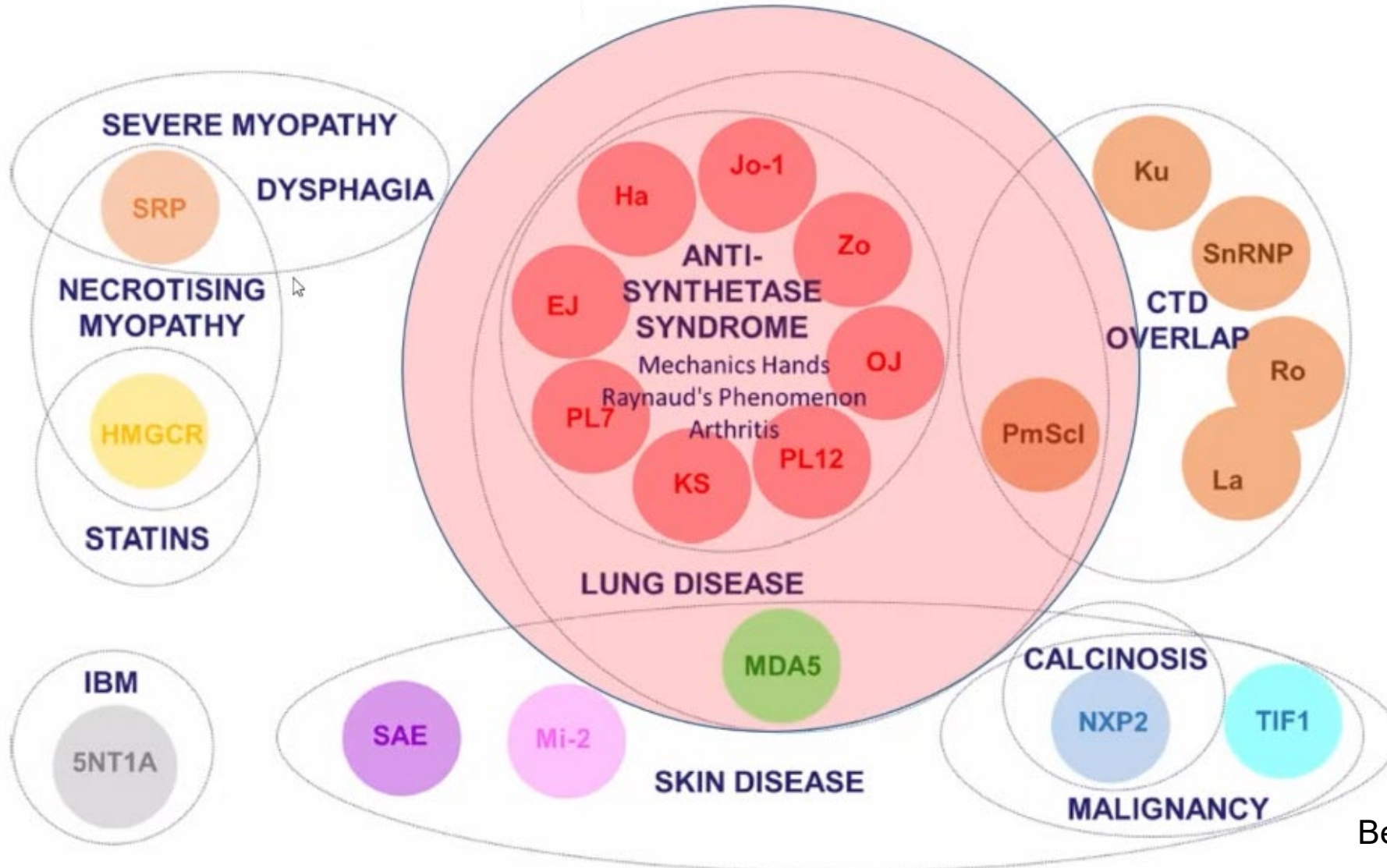
Norwegian cohort of SSc-ILD patients, **causes of death** segregated into **respiratory** and **non-respiratory**

- **132/323 (41%) SSc-ILD patients deceased, causes of death available for 99 (76%)**
- 24/99 patients (24%) died of respiratory causes: 2/3 respiratory tract infections and 1/3 respiratory failure
 - 12/24 had FVC \geq 70%, cause of death was respiratory tract infections in 9/12

Conclusion: a significant proportion of SSc-ILD patients who died of respiratory causes had preserved lung function and did not progress to more severe, end-stage lung disease

A. M. Hoffmann-Vold et al, Ann Rheum Dis 2024; 83 (supplement 1): 334

ILD in Myositis



MDA5-positive Myositis

- Skin disease without muscle / lung involvement
- Chronic skin disease with ILD similar to antisynthetase syndrome
- Severe skin disease with rapidly-progressive ILD (RPILD)
 - Deterioration of interstitial changes on HRCT with progression of dyspnea and hypoxemia within one month after first manifestation of respiratory symptoms
 - Mortality up to 80% even if diagnosed early and/or despite intensive immunosuppressive therapy
 - Biomarkers associated with an unfavorable disease course
 - Ferritin levels \geq (500-)1000 ng/ml
 - Elevated CRP
 - Elevated LDH
 - Age >60 years
 - High titres of Anti-MDA5 (ELISA)
 - Anti-SSA (Ro52)



Sjögren-Disease associated ILD

- Often underrecognized
 - Affects up to 20-25% (6-70%)
- ILD may precede the development of other symptoms
- Risk factors
 - Older age, male sex, disease duration, smoking, increase in ANA or RF titre + presence of anti-SSA (Ro52), low C3, increase in CRP, non-sicca syndrome
- HRCT pattern
 - NSIP 45%, UIP 16%, LIP 15%, OP 11%
- Increased risk of lymphoma
 - Cumulative risk of 3.4% and 9.8% at 5 and 15 years from diagnosis
 - Lymphoma of the lungs in approx. 6%
 - Consider biopsy

Luppi F, et al. Clin Exp Rheumatol 2020; 38: S291-S300

Luppi F, Sebastiani M, Sverzellati N, et al. Eur Respir Rev 2020; 29: 200021

Lee AS, et al. Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjögren's. CHEST 2021; 159(2):683-698

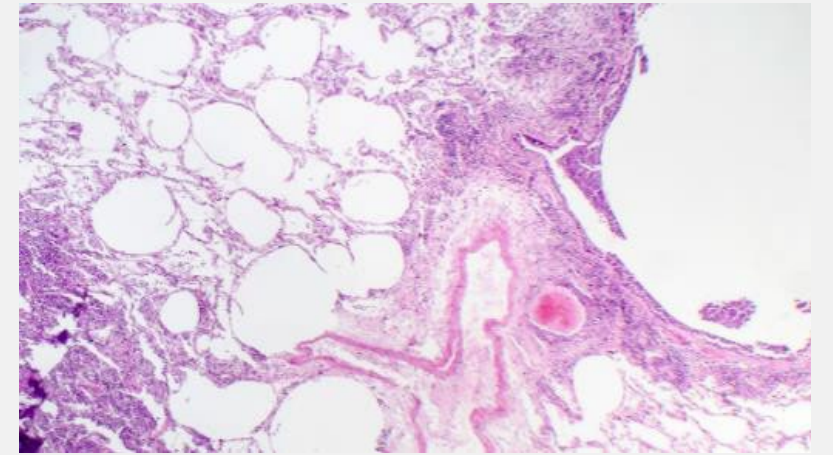
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ERS/EULAR guidelines for the management of CTD-ILD

Ongoing Task Forces

ERS Task Forces work to produce official guidelines, statements and technical standards on specific topics in respiratory medicine, in order to guide other respiratory professional in their clinical practice



TF-2020-03

ERS/EULAR Clinical practice guideline on connective tissue diseases with interstitial lung (ILD) involvement

Katerina Antoniou,
Bruno Crestani,
Anna-Maria Hoffmann-Vold,
Oliver Distler

2023 ACR/CHEST guideline for the screening and monitoring of SARD-ILD

Arthritis & Rheumatology

Vol. 76, No. 8, August 2024, pp 1201-1213

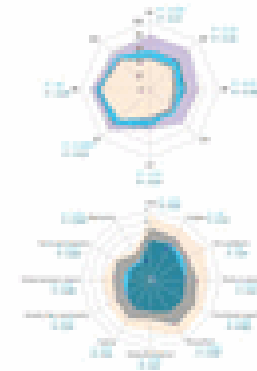
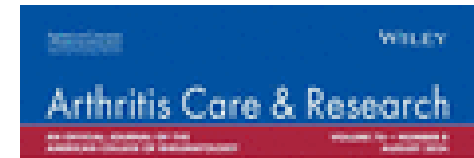
DOI 10.1002/art.42860

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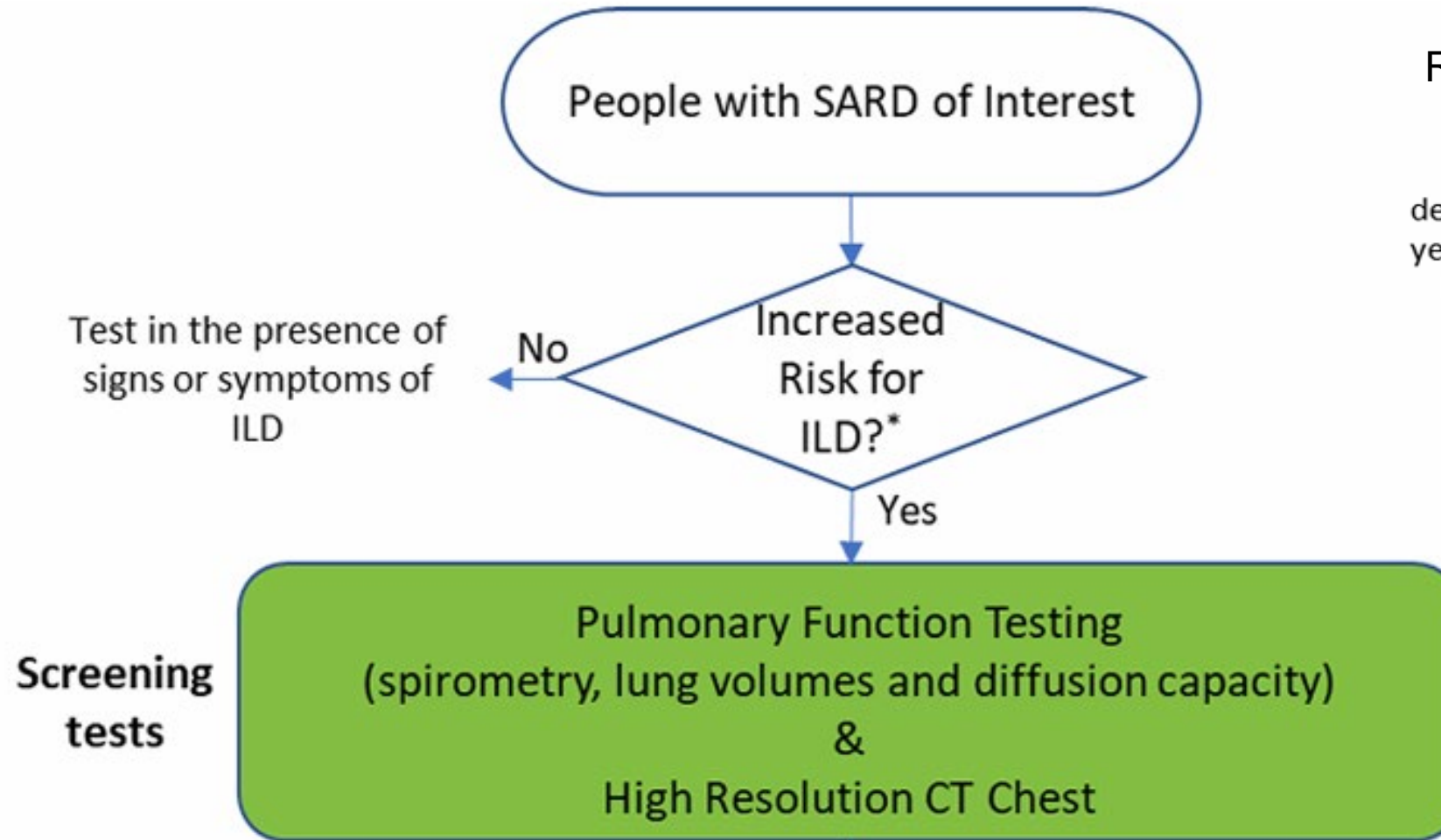
2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Screening and Monitoring of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases

Sindhu R. Johnson,^{1+*} Elana J. Bernstein,^{2*} Marcy B. Bolster,³ Jonathan H. Chung,⁴ Sonye K. Danoff,⁵ Michael D. George,⁶ Dinesh Khanna,⁷ Gordon Guyatt,⁸ Reza D. Mirza,⁸ Rohit Aggarwal,⁹ Aberdeen Allen Jr,¹⁰ Shervin Assassi,¹¹ Lenore Buckley,¹² Hassan A. Chami,⁵ Douglas S. Corwin,¹³ Paul F. Dellaripa,¹⁴ Robyn T. Domsic,⁹ Tracy J. Doyle,¹⁴ Catherine Marie Falardeau,¹⁵ Tracy M. Frech,¹⁶ Fiona K. Gibbons,³ Monique Hinchcliff,¹² Cheilonda Johnson,⁶ Jeffrey P. Kanne,¹⁷ John S. Kim,¹⁸ Sian Yik Lim,¹⁹ Scott Matson,²⁰ Zsuzsanna H. McMahan,⁵ Samantha J. Merck,²¹ Kiana Nesbitt,²² Mary Beth Scholand,²³ Lee Shapiro,²⁴ Christine D. Sharkey,¹⁷ Ross Summer,²⁵ John Varga,⁷ Anil Warriar,²⁶ Sandeep K. Agarwal,²⁷ Danielle Antin-Ozerkis,¹² Bradford Bemiss,²⁸ Vaidehi Chowdhary,¹² Jane E. Dematte D'Amico,²⁸ Robert Hallowell,³ Alicia M. Hinze,²⁹ Patil A. Injean,³⁰ Nikhil Jiwrajka,⁶ Elena K. Joerns,³¹ Joyce S. Lee,³² Ashima Makol,²⁹ Gregory C. McDermott,¹⁴ Jake G. Natalini,³³ Justin M. Oldham,⁷ Didem Saygin,⁹ Kimberly Showalter Lakin,³⁴ Namrata Singh,³⁵ Joshua J. Solomon,³⁶ Jeffrey A. Sparks,¹⁴ Marat Turgunbaev,³⁷ Samera Vaseer,³⁸ Amy Turner,³⁷ Stacey Uhl,³⁹ and Ilya Ivlev³⁹



[2023 American College of Rheumatology \(ACR\)/American College of Chest Physicians \(CHEST\) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases \(wiley.com\)](https://www.wiley.com)

Screening for SARD-ILD



Re-screening:

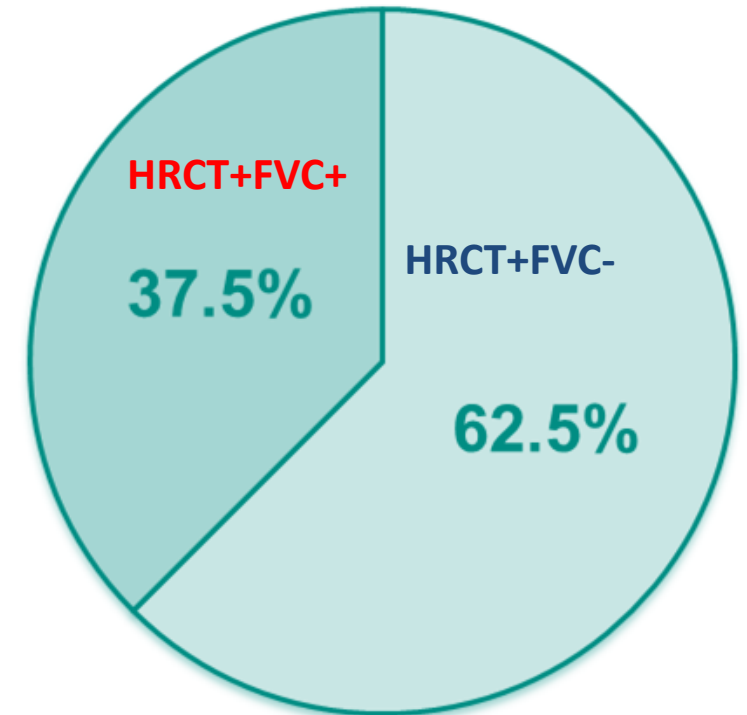
Test if signs or symptoms of ILD develop and consider yearly re-screening in high-risk patients

Cave!

Pulmonary function testing alone misses the majority of patients with SSc-ILD

102 SSc patients (Zurich cohort)

- 64/102 (63%) with significant ILD on HRCT
- 27/102 (26%) with FVC <80% predicted
- only 20/64 (37.5%) with significant ILD and FVC <80% predicted



Risk factors for SARD-ILD

Systemic sclerosis:

- anti-Sc170, nucleolar ANA, dcSSc, male sex, African American race, early disease (<5–7y), acute phase reactants

Idiopathic inflammatory myopathies:

- anti-synthetase (Jo-1, PL7, PL12, EJ, OJ, KS, Ha, Zo), anti-MDA-5, anti-Ku, anti Pm/Scl, anti-Ro52 positivity; mechanic's hands, arthritis/arthralgia, ulcerating lesions

Mixed connective tissue disease:

- dysphagia, Raynauds, other SSc clinical or laboratory features

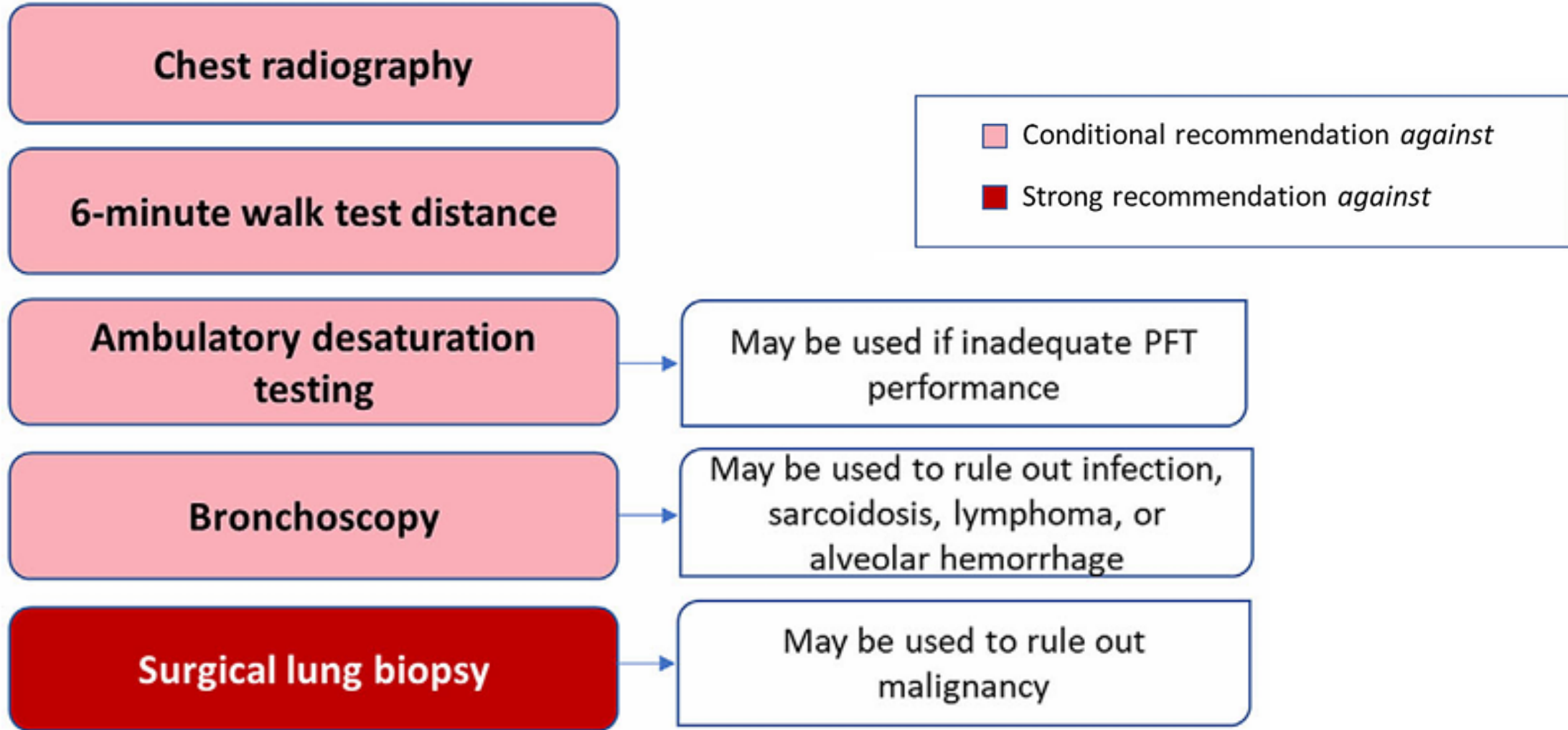
Rheumatoid arthritis:

- high-titer RF and/or anti-CCP, smoking, older age at onset, high disease activity, male sex, higher BMI

Sjögren disease:

- anti-Ro52, Raynaud phenomenon, older age, lymphopenia, severe dental caries

Screening tests recommended *against*



Monitoring SARD-ILD

Monitoring tests

Pulmonary Function Testing
(spirometry, lung volumes and diffusion capacity)

IIM: every 3-6 months the 1st year,
then less frequently once stable

SSc: every 3-6 months the 1st year,
then less frequently once stable

RA/SjD/MCTD: every 3-12 months the 1st year,
then less frequently once stable

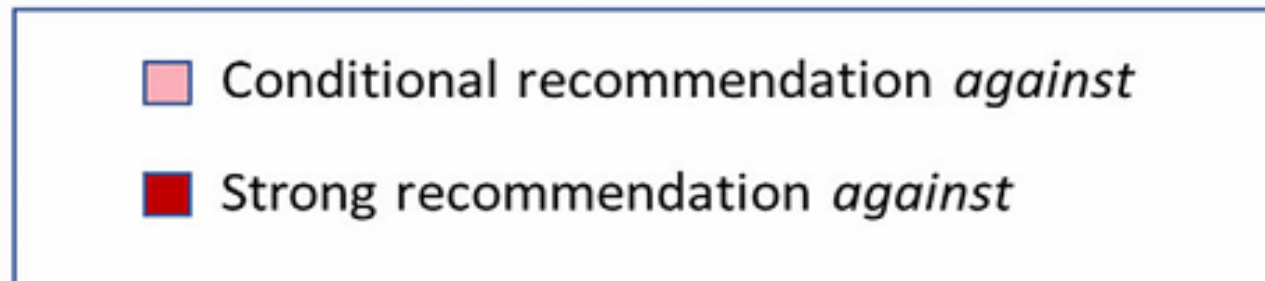
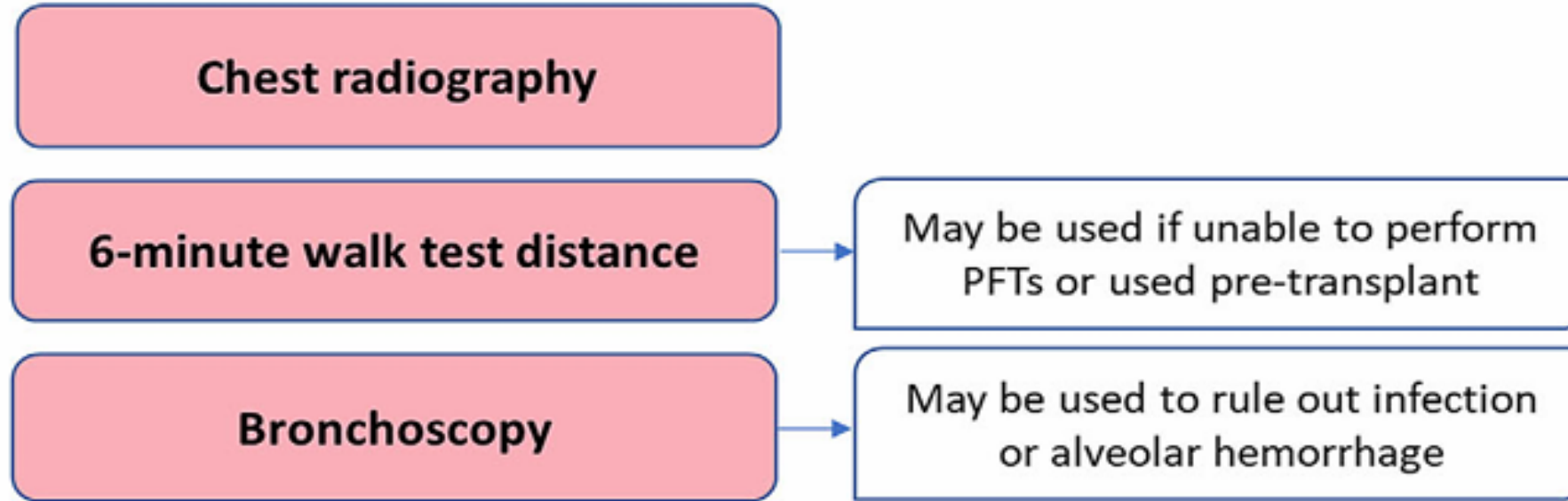
&

Ambulatory Desaturation Testing every 3-12 months[†]

&

High Resolution CT Chest as needed

Monitoring tests recommended *against*



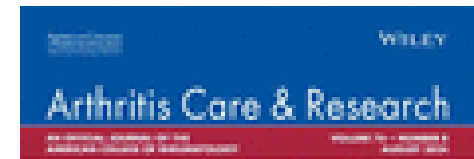
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2023 ACR/CHEST guideline for the treatment of SARD-ILD

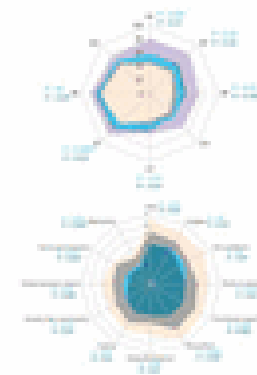
Arthritis Care & Research
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ACR/CHEST guidelines for first line therapy in SARD-ILDs

	Systemic Sclerosis	Myositis	MCTD	Rheumatoid Arthritis	Sjögren's
First-line ILD therapy	Preferred Mycophenolate [†] Tocilizumab Rituximab	Preferred Mycophenolate [†] Azathioprine Rituximab CNI	Preferred Mycophenolate [†] Azathioprine Rituximab	Preferred Mycophenolate [†] Azathioprine Rituximab	Preferred Mycophenolate [†] Azathioprine Rituximab
	Additional options Cyclophosphamide Nintedanib Azathioprine	Additional options JAKi Cyclophosphamide	Additional options Tocilizumab Cyclophosphamide	Additional options Cyclophosphamide	Additional options Cyclophosphamide
+ Glucocorticoids	Strong recommendation against GCs	Short-term GCs*	Short-term GCs*	Short-term GCs*	Short-term GCs*

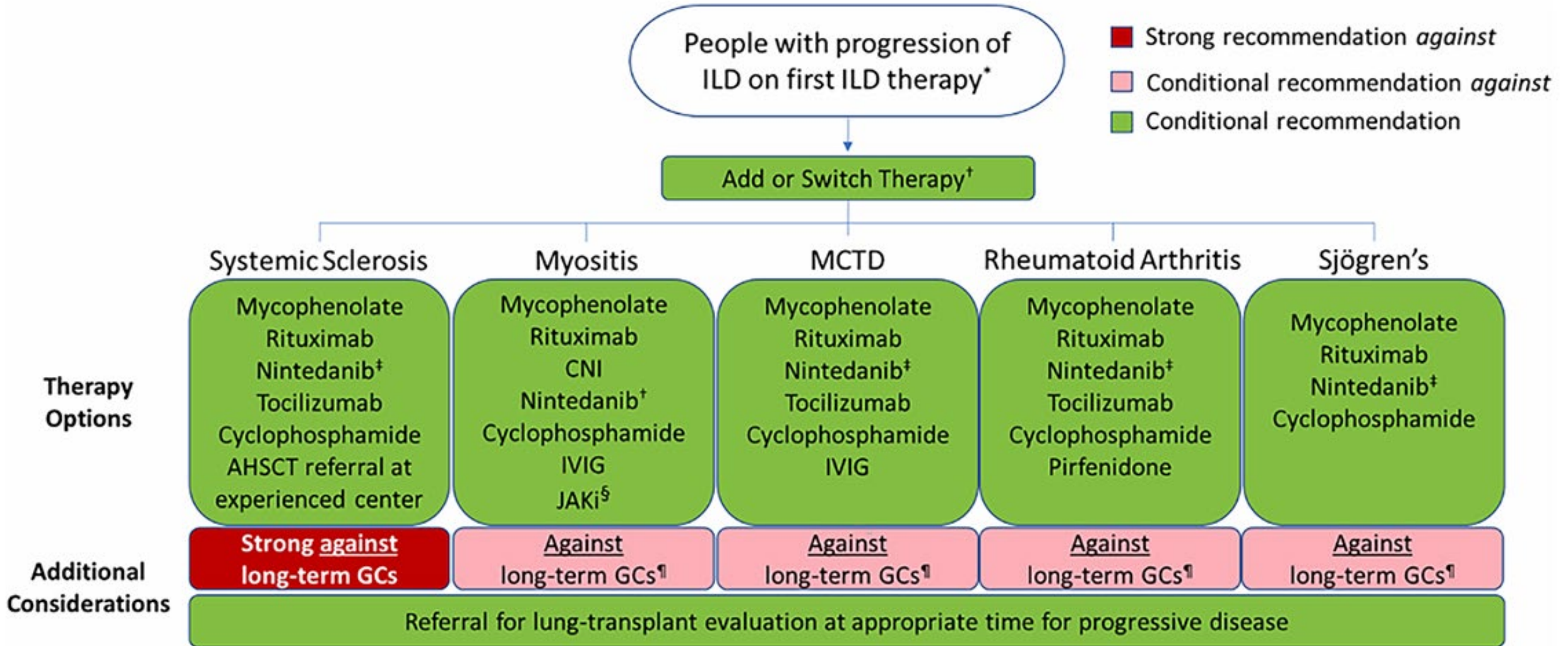
■ Strong recommendation *against* ■ Conditional recommendation

All SARD-ILD: conditional recommendation against leflunomide, methotrexate, TNFi, and abatacept as first-line option.

Treatment decisions will depend on specific situations and patient factors.

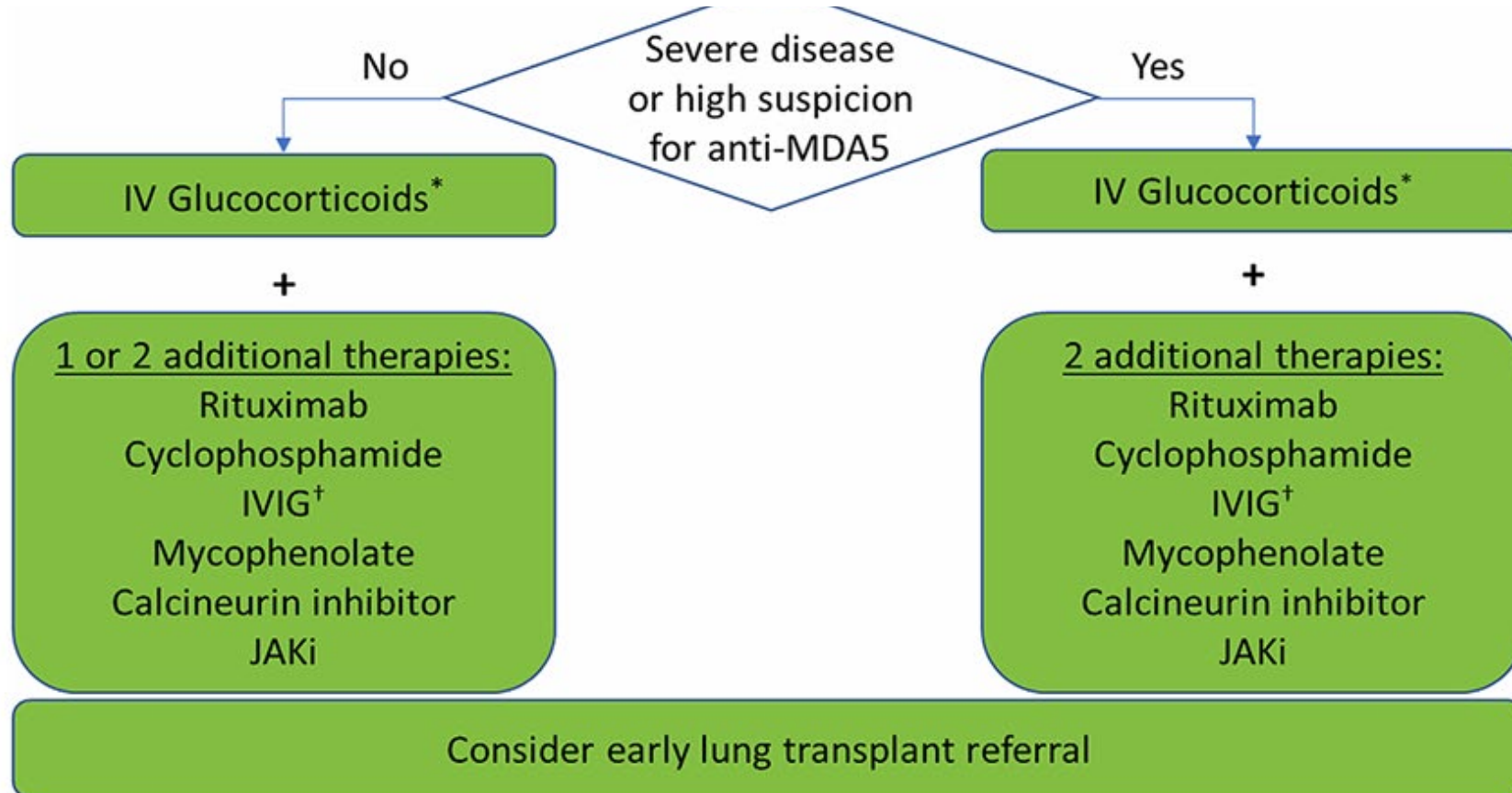
*Decisions on glucocorticoid dose and oral vs intravenous administration depend on disease severity. Glucocorticoids should be used with caution in patients with MCTD and an SSc phenotype who may be at increased risk of renal crisis. ACR, American College of Rheumatology; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; JAK, janus kinase; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; SARD-ILD, systemic autoimmune rheumatic disease-associated interstitial lung disease; SJS, Sjögren's syndrome; SSc, systemic sclerosis American College of Rheumatology. Summary: 2023 ILD Guideline – Treatment. Available at: <https://rheumatology.org/interstitial-lung-disease-guideline> (accessed September 2023)

ACR/CHEST guidelines for second-line therapy in SARD-ILDs

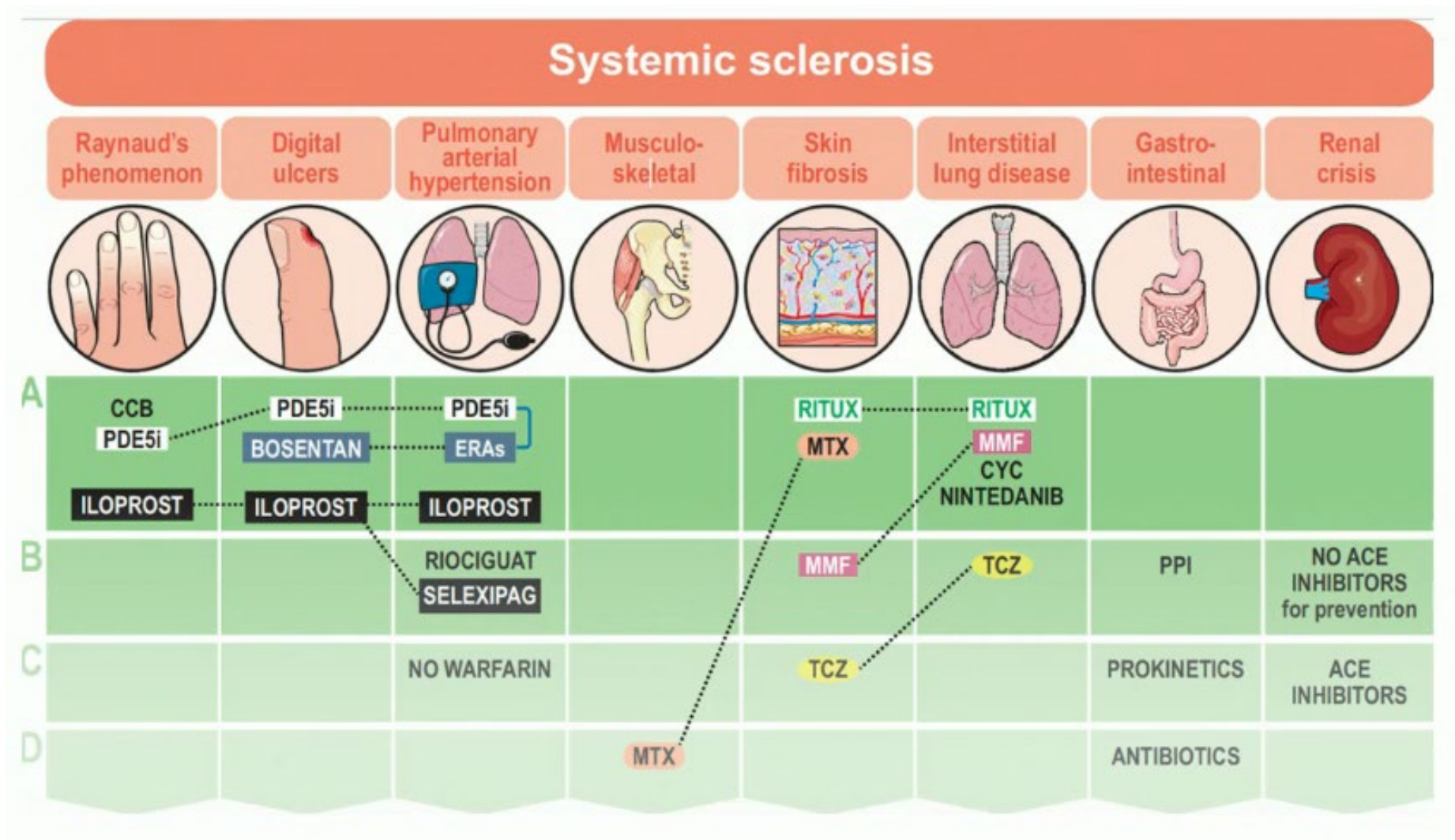


ACR/CHEST guidelines for therapy in rapidly progressive ILD

= rapid progression from breathing room air (or a patient's baseline O2 requirement) to a high O2 requirement or intubation within days to weeks, without a documented alternative cause (eg, infection, heart failure),



EULAR recommendations for the treatment of SSc



Systemic sclerosis

Raynaud's phenomenon

Digital ulcers

Pulmonary hypertension

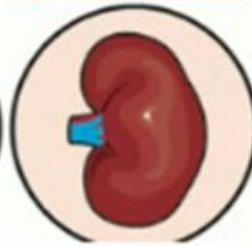
Skin fibrosis

Interstitial lung disease

Musculo-skeletal

Gastro-intestinal

Renal crisis



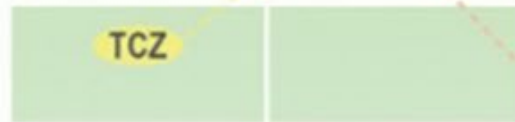
A



B



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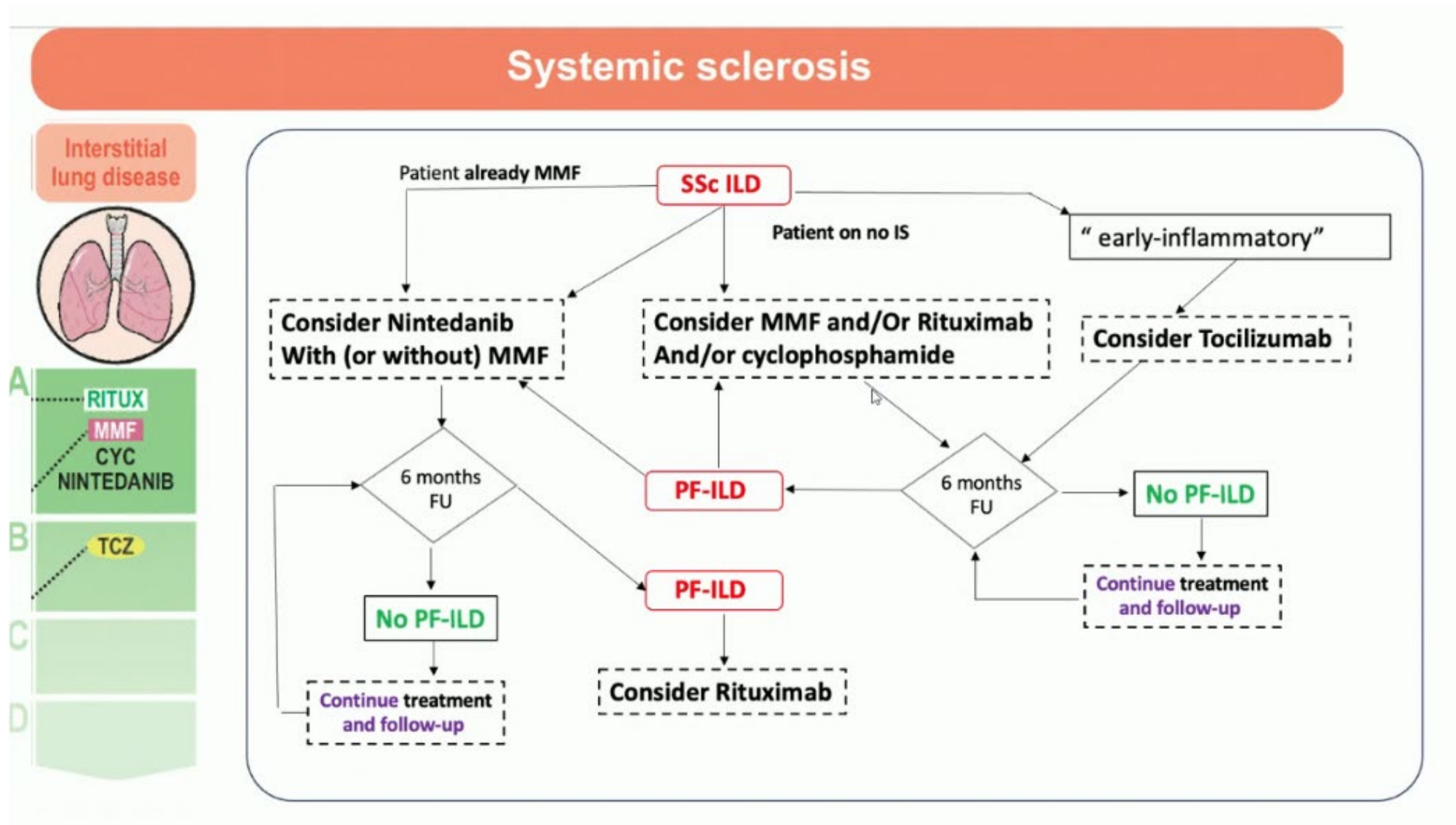


D



The immune suppression continuum across skin and lung fibrosis

EULAR recommendations for the treatment of SSc



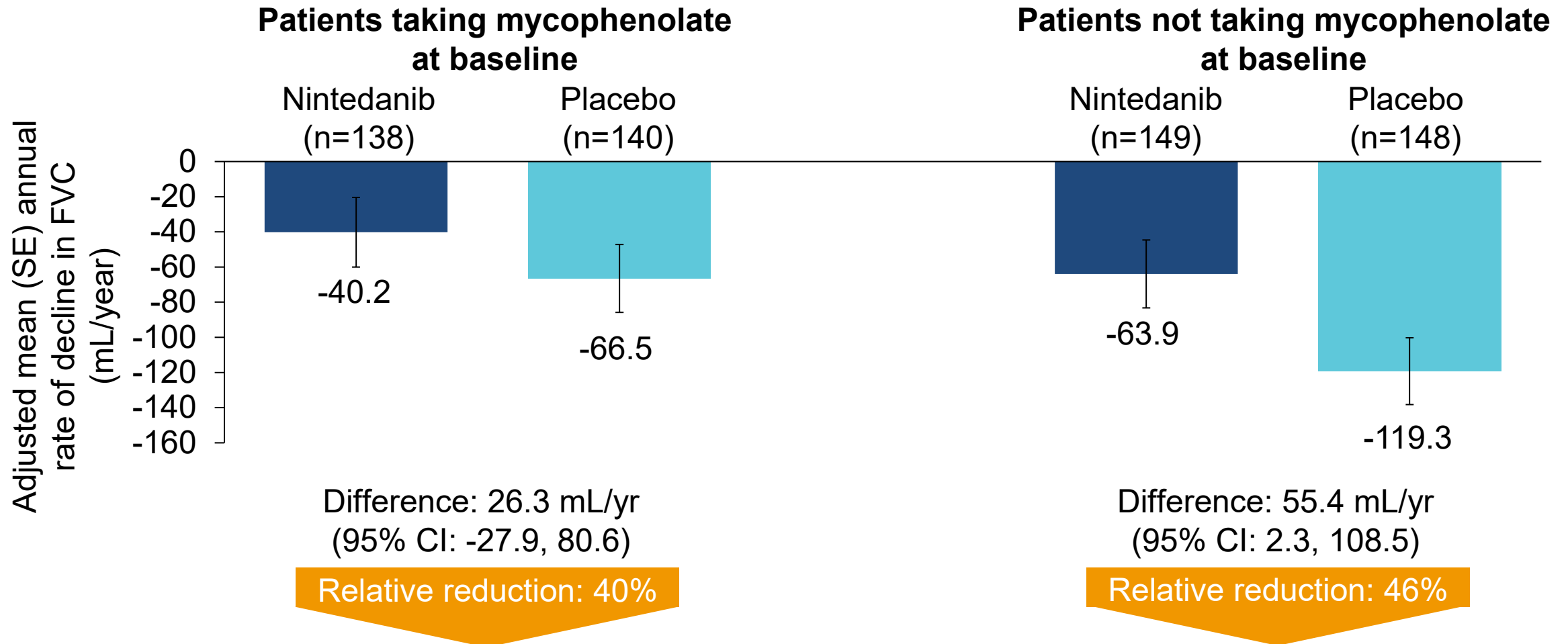
Nintedanib Therapy Alone and Combined with Mycophenolate in Patients with SSc-ILD: Systematic Review and Meta-analysis

3 studies:

- **SENSCIS:** Highland KB, et al. Efficacy and safety of nintedanib in patients with SSc-ILD treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *Lancet Respir Med* 2021;9:96–106.
- **SENSCIS-ON:** Allanore Y, et al. Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. *Ann Rheum Dis*. 2022 Dec;81(12):1722-1729.
- **INBUILD:** Wells AU, et al. Nintedanib in patients with progressive fibrosing ILDs (PPF) - subgroup analyses by ILD diagnosis in the INBUILD trial. *Lancet Respir Med*. 2020 May;8(5):453-460.

Conclusion: changes in the annual rate of decline in FVC favored combination therapy over placebo (mean difference, 79.1 ml)

SENSCIS: rate of decline in FVC (mL/year) over 52 weeks in subgroups by use of mycophenolate at baseline



Treatment-by-time-by-subgroup interaction p=0.45.
Highland KB et al. Lancet Respir Med 2021;9:96–106.

Rituximab in Patients with Systemic Sclerosis-associated Interstitial Lung Disease: A Systematic Review and Meta-Analysis

3 studies selected:

- **DESIREs**: Ebata S, et al. Safety and efficacy of rituximab in SSc (DESIREs): a double-blind, investigator-initiated, randomised, placebo-controlled trial. *Lancet Rheumatol.* 2021 Jul;3(7):e489-e497.
 - **RTX effective and safe in SSc, significant effect on mRSS and FVC => approval for SSc in Japan**
- **EVER-ILD**: Mankikian J, et al Rituximab and mycophenolate mofetil combination in patients with ILD (EVER-ILD): a double-blind, randomised, placebo-controlled trial. *Eur Respir J.* 2023 Jun 8;61(6):2202071
 - **MMF+RTX superior to MMF+PBO in ILD of NSIP pattern (CTD-ILD or IPF)**
- **RECITAL**: Maher TM, et al. Rituximab vs. intravenous cyclophosphamide in patients with CTD-ILD in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. *Lancet Respir Med.* 2023 Jan;11(1):45-54
 - **RTX was not superior to CYC in CTD-ILD**

Conclusions of the metaanalysis:

- **RTX significantly improved FVC% predicted (mean difference, 3.13; 95% confidence interval [CI], 0.37 to 5.90) and mRSS (mean difference, -7.01; 95% CI, 11.46 to -2.56) at 24-48 week**
- **quality of evidence very low (by the GRADE approach)**

Interstitielle Lungenerkrankungen und Rheuma

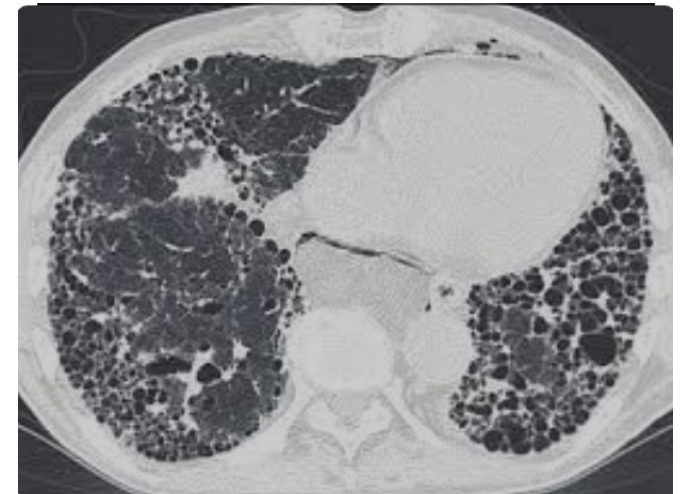
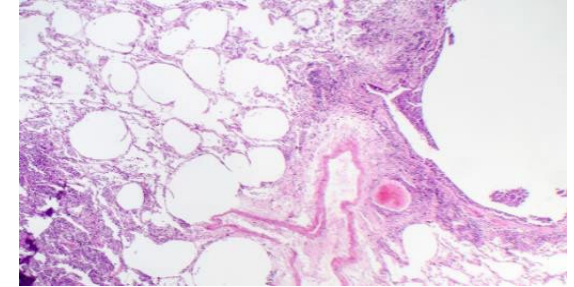
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Role of the general internal medicine specialist in the care of SARD-ILD

- Drug safety monitoring
 - All non-biologics: blood count, liver function tests
 - Biologics: same as above for tocilizumab
 - History of diverticulitis contraindicates tocilizumab!
 - Nintedanib: gastro-intestinal adverse events, diarrhea, dehydration
 - Glucocorticoids: (monitoring adverse events, weight, blood pressure, HbA1c, etc.), tapering
- Vaccination (pre-treatment and yearly) for patients receiving immunosuppressive medicines – cave Rituximab!
- Monitoring of infections/SARD-ILD exacerbations
- Interdisciplinary care GP/rheumatologist/pneumologist

Take-home messages

- **SARD-ILD have a severe outcome**
- **Screening for SARD-ILD:** adapted to each disease
 - High resolution chest CT is crucial for diagnosis
 - Lung function test are part of the initial screening and of monitorization
- **Treatment adapted to each SARD and to risk profile (progression, antibodies)**
 - MMF, CYC etc.
 - Biologic agents: Tocilizumab, Rituximab
 - JAK inhibitors
 - Nintedanib (RA-ILD: Pirfenidone)
 - Glucocorticoids, IVIG
- **Interdisciplinary care to monitor safety and efficacy**





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