

Interstitial lung disease as the initial manifestation of systemic autoimmune disease: a narrative review of autoantibodies, biomarkers, prognosis, and management

H.M. Moutsopoulos

Science Section, National Academy of Athens, Greece.

Haralampos M. Moutsopoulos, MD, FACP, FRCP (hc), Master ACR

Please address correspondence to: National Academy of Athens, Science Section, 28 Panepistimiou Street, 10679 Athens, Greece.

E-mail: hmoutsop@med.uoa.gr

Received on July 19, 2026; accepted in revised form on September 28, 2026.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2026.

Key words: interstitial lung disease, interstitial pneumonia with autoimmune features, connective tissue disease, autoantibodies, progressive pulmonary fibrosis, therapies

ABSTRACT

Interstitial lung disease (ILD) may be the first or only clinically apparent manifestation of systemic autoimmune rheumatic disease (SARD), preceding extrapulmonary features by months or years. The European Respiratory Society/American Thoracic Society research classification of interstitial pneumonia with autoimmune features (IPAF) provides a framework for patients with interstitial pneumonia and autoimmune features who do not meet criteria for a defined SARD. Importantly, IPAF requires features from at least two of three domains – clinical, serologic, and morphologic – and cannot be assigned on autoantibody positivity alone. Extended, phenotype-directed autoantibody testing can reveal lung-dominant anti-synthetase syndrome, clinically amyopathic dermatomyositis, early systemic sclerosis, rheumatoid arthritis, or Sjögren's syndrome (Autoimmune epithelitis). Prognosis is heterogeneous and is driven more consistently by the fibrotic burden, usual interstitial pneumonia pattern, baseline and longitudinal pulmonary physiology, and comorbidities than by the IPAF label itself. KL-6, surfactant protein D, CCL18, MMP-7, and multiplex proteomic signatures are promising biomarkers, but none is sufficiently validated to replace serial high-resolution computed tomography and pulmonary function testing. Management should be individualised through multidisciplinary discussion. Immunomodulation is most defensible for inflammatory or SARD-like phenotypes, whereas antifibrotic therapy should be considered when progressive pulmonary fibrosis is established despite appropriate management. IPAF should therefore be viewed as a dynamic research phenotype within a contin-

uum of lung-dominant autoimmunity, requiring longitudinal reassessment for evolution to a defined SARD.

Introduction

Interstitial lung disease (ILD) may precede, accompany, or remain the sole manifestation of a systemic autoimmune rheumatic disease (SARD). In 2015, the European Respiratory Society and American Thoracic Society introduced the term interstitial pneumonia with autoimmune features (IPAF) to standardise research in patients with idiopathic interstitial pneumonia who show evidence of autoimmunity but do not fulfill classification criteria for a defined SARD (1). IPAF is a research classification, not a clinical diagnosis or a distinct disease entity.

Classification requires: (i) interstitial pneumonia demonstrated by high-resolution computed tomography (HRCT) or surgical lung biopsy; (ii) exclusion of alternative causes; (iii) failure to meet criteria for a defined SARD; and (iv) at least one feature from at least two of three domains – clinical, serologic, and morphologic (1). This distinction is clinically important because isolated autoantibody positivity is insufficient. The framework has improved cohort standardisation and promoted pulmonology-rheumatology collaboration, although its heterogeneity and the omission or weighting of some features remain debated (2-4).

Autoantibodies in lung-dominant autoimmunity

Autoantibodies may precede extrapulmonary manifestations and can provide the earliest clue to an occult SARD. Testing should be guided by the clinical and radiologic phenotype rather than applied indiscriminately. Antinu-

Competing interests: none declared.

Table I. Autoantibodies relevant to isolated or lung-dominant autoimmune ILD.

Autoantibody	Typical association	Interpretive implication
Anti-Jo-1, PL-7, PL-12, EJ, OJ	Antisynthetase syndrome	ILD can precede myositis or arthritis; expand myositis evaluation.
Anti-MDA5	Dermatomyositis spectrum	Signals risk of rapidly progressive ILD; urgent phenotype assessment.
Anti-Ro52	Myositis, Sjögren disease, systemic sclerosis	Often a severity modifier when coexisting with disease-specific antibodies; isolated positivity is non-specific.
ANA (titre and pattern)	Multiple SARDs	Nucleolar or centromere patterns are more informative than low-titre non-specific positivity.
Rheumatoid factor; anti-CCP	Rheumatoid arthritis	ILD may precede articular disease; anti-CCP is more specific.
Anti-Scl-70; anticentromere	Systemic sclerosis	May precede overt skin disease; assess Raynaud phenomenon and nailfold capillaries.
Anti-PM/Scl; anti-Ku; anti-U1-RNP	Overlap syndromes / mixed connective tissue disease	Supports longitudinal surveillance for evolving systemic manifestations.
ANCA (outside IPAF serologic domain)	ANCA-associated vasculitis	Consider a distinct diagnostic pathway, especially with UIP, hematuria, or systemic vasculitic features.

Table II. Candidate biomarkers and established clinical predictors in IPAF.

Marker / approach	Biological domain	Potential clinical value	Current limitation
KL-6	Alveolar epithelial injury/regeneration	Correlates with ILD presence and burden; cut-offs vary by population and assay.	Not validated as a stand-alone IPAF progression test.
Surfactant protein D	Type II pneumocyte / surfactant injury	May track pulmonary involvement and activity.	Limited IPAF-specific validation.
CCL18	Macrophage-driven profibrotic signalling	Associated with fibrotic progression in several ILDs.	No universally accepted treatment threshold.
MMP-7	Epithelial injury and matrix remodelling	Prognostic signal in IPF and fibrosing ILD.	Evidence is largely extrapolated to IPAF.
Multiprotein panels	Integrated injury, immune, vascular, and matrix pathways	Potentially improves multidimensional risk prediction.	Requires external validation and assay standardisation.
Neutrophil count	Systemic inflammatory signal	Independent association with 1-year progression in one prospective IPAF cohort.	Non-specific; interpret with infection and treatment context.
Fibrotic HRCT phenotype	Structural fibrosis, especially UIP	Consistent clinical predictor of progression and mortality.	Requires expert radiologic and multidisciplinary interpretation.

Continuum of lung-dominant systemic autoimmunity

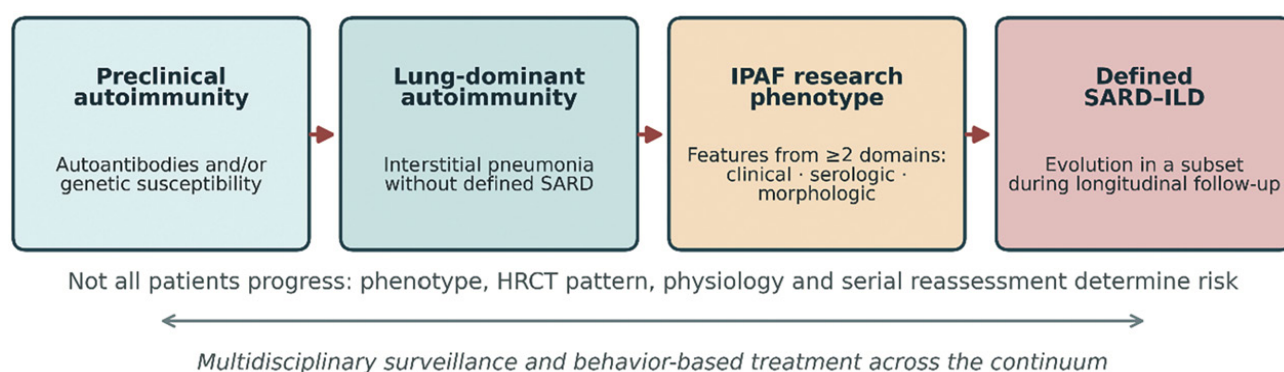


Fig. 1. Proposed continuum of lung-dominant systemic autoimmunity. Autoantibodies and susceptibility may precede isolated interstitial pneumonia. Patients who do not meet criteria for a defined systemic autoimmune rheumatic disease (SARD) may fulfill the IPAF research classification only when features are present in at least two of the three clinical, serologic, and morphologic domains. A subset evolves to defined SARD-associated ILD; many do not. Multidisciplinary longitudinal reassessment is therefore required across the continuum.

clear antibody (ANA) titre and pattern are relevant: nucleolar and centromere patterns increase suspicion for systemic sclerosis, whereas low-titre non-specific

ANA is common and should be interpreted cautiously. High-titre rheumatoid factor and anti-cyclic citrullinated peptide antibodies support rheumatoid

autoimmunity, and ILD may precede clinically apparent arthritis (5-8). Myositis-specific and myositis-associated antibodies are particularly important.

Table III. Behaviour- and phenotype-based management of IPAF.

Strategy	Most defensible setting	Role	Key caveats / monitoring
Observation and surveillance	Mild, stable disease without clear progression	Avoids unnecessary toxicity	Scheduled symptoms, PFTs, oxygenation/exercise testing, HRCT as indicated, and rheumatologic reassessment.
Glucocorticoids	Inflammatory ILD or acute worsening after infection is excluded	Rapid anti-inflammatory effect	Minimise dose/duration; infection, bone, metabolic, and cardiovascular toxicity.
Mycophenolate / azathioprine	SARD-like inflammatory or mixed phenotype	Steroid-sparing maintenance; observational IPAF support	CBC, liver tests; mycophenolate GI and reproductive toxicity; azathioprine pharmacogenetic considerations.
Tacrolimus	Selected myositis-spectrum or refractory inflammatory ILD	Potential benefit in specialist practice	Renal function, blood pressure, drug levels, interactions; limited IPAF evidence.
Rituximab / cyclophosphamide	Severe, rapidly progressive, or refractory autoimmune ILD	Escalation options supported mainly by CTD-ILD evidence	Infection screening/prophylaxis; immunoglobulins for rituximab; fertility, bladder, and malignancy risks for cyclophosphamide.
JAK inhibitor	Selected anti-MDA5 or refractory myositis-associated ILD	Emerging phenotype-specific option	Not standard for unselected IPAF; infection, thrombosis, and cardiovascular risk assessment.
Nintedanib	Established progressive pulmonary fibrosis phenotype	Slows FVC decline	Diarrhoea, liver tests, bleeding risk; does not establish or treat systemic autoimmunity.

CBC: complete blood count; PFTs: pulmonary function tests

Antisynthetase antibodies (including anti-Jo-1, PL-7, PL-12, EJ, and OJ) may identify lung-dominant antisynthetase syndrome before myositis or inflammatory arthritis becomes evident. Anti-MDA5 is associated with clinically amyopathic dermatomyositis and rapidly progressive ILD. Anti-Ro52 frequently coexists with other autoantibodies and, particularly in myositis-spectrum disease, is associated with more severe ILD; however, isolated anti-Ro52 is not disease-specific and must be interpreted in context (9-13). Anti-topoisomerase I, anti-centromere, anti-PM/Scl, anti-Ku, and anti-U1-RNP may indicate systemic sclerosis or overlap disease before a fully classifiable systemic phenotype emerges (Table I)(14, 15).

Biomarkers and prediction of progression

IPAF shares biological features with both SARD-associated ILD and idiopathic pulmonary fibrosis (IPF). Most biomarker evidence is therefore extrapolated from these neighbouring populations, and IPAF-specific validation remains limited. Serum KL-6 and surfactant protein D reflect alveolar epithelial injury and correlate with ILD burden in several autoimmune ILD cohorts. CCL18 and MMP-7 represent macrophage-associated profibrotic activity and epithelial remodelling, re-

spectively. Multiplex proteomics may improve risk stratification by integrating epithelial injury, inflammation, extracellular-matrix turnover, and vascular biology, but standardised assays and clinically actionable thresholds are not yet established (16-19).

Recent prospective data reinforce the primacy of clinical and radiologic variables. Approximately one-third of patients in one IPAF cohort progressed within one year; higher peripheral neutrophil counts and fibrotic HRCT features were independent predictors (20). Across studies, usual interstitial pneumonia (UIP), greater fibrotic extent, lower baseline forced vital capacity (FVC) or diffusing capacity for carbon monoxide (DLCO), and subsequent physiological decline identify higher-risk patients (21-24). Conversely, organising pneumonia or NSIP-organising pneumonia overlap may show greater treatment responsiveness (22). Biomarkers should therefore complement – not replace – serial pulmonary function tests, HRCT, exercise assessment, and multidisciplinary review (Table II).

Prognosis and longitudinal evolution

The natural history of IPAF is variable. Outcomes are often intermediate between those of IPF and SARD-associated ILD, but this summary obscures

substantial phenotype-dependent differences. A UIP-pattern IPAF phenotype may behave similarly to IPF, whereas NSIP, organising pneumonia, and NSIP-organising pneumonia overlap more often resemble inflammatory SARD-associated ILD (21-24). Comorbidity burden also modifies progression and survival and should be incorporated into risk assessment (25).

A minority of patients eventually meet criteria for a defined SARD, most often inflammatory myopathy, systemic sclerosis, rheumatoid arthritis, or Sjögren disease (Fig. 1). The reported proportion varies with cohort composition, follow-up duration, and intensity of rheumatologic reassessment. Younger age, disease-specific autoantibodies, Raynaud phenomenon, inflammatory arthritis, mechanic's hands, and systemic-sclerosis-pattern nailfold capillary abnormalities increase diagnostic suspicion. Nailfold videocapillaroscopy is not part of the current IPAF criteria, but it can reveal occult systemic sclerosis-spectrum microangiopathy and should be considered when clinically indicated (26).

Management

No therapy is approved specifically for IPAF, and randomised treatment trials in this population are scarce. Management should be determined by multidisciplinary discussion and

should integrate the dominant phenotype (inflammatory vs. fibrotic), HRCT pattern, disease severity, trajectory, extrapulmonary features, comorbidities, infection risk, and patient preferences. Stable, mild disease may be observed with structured surveillance rather than treated immediately.

For clinically significant inflammatory or SARD-like disease, glucocorticoids may be used for induction when rapid anti-inflammatory activity is required, with a steroid-sparing agent such as mycophenolate mofetil, azathioprine, or – in selected phenotypes – tacrolimus. Mycophenolate is commonly favored because of its experience base and tolerability, although direct IPAF evidence is observational (27-29). Rituximab or cyclophosphamide may be considered for severe, rapidly progressive, or refractory autoimmune ILD; the RE-CITAL trial informs CTD-ILD practice but was not an IPAF-specific trial (30, 31). JAK inhibitors are promising particularly for anti-MDA5-associated rapidly progressive ILD, but evidence cannot yet support their routine use in unselected IPAF.

When progressive pulmonary fibrosis develops despite appropriate management, nintedanib should be considered according to the progressive pulmonary fibrosis framework. The INBUILD trial demonstrated reduced FVC decline across progressive fibrosing ILDs, and SENSICIS established benefit in systemic sclerosis-associated ILD; neither trial makes IPAF itself an indication independent of progressive behaviour (32-34). Combined immunomodulatory and antifibrotic treatment may be rational when inflammatory autoimmunity and progressive fibrosis coexist, but sequencing and monitoring should be individualised (Table III).

Conclusions

Isolated ILD can be the earliest manifestation of systemic autoimmunity. IPAF provides a useful research framework, but it should not be equated with autoantibody-positive ILD or treated as a single disease. Extended autoantibody testing, careful evaluation for subtle extrapulmonary features, expert HRCT interpretation, and longitudi-

nal multidisciplinary reassessment can identify patients with lung-dominant or evolving SARD. Prognosis and treatment should be driven by phenotype and behaviour: inflammatory features support immunomodulation, whereas established progressive pulmonary fibrosis supports antifibrotic therapy. Future studies should validate integrated serologic, proteomic, imaging, and physiological models that predict both fibrotic progression and evolution to a defined systemic disease.

References

1. FISCHER A, ANTONIOU KM, BROWN KK *et al.*: An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J* 2015; 46: 976-87. <https://doi.org/10.1183/13993003.00150-2015>
2. JOERNS EK, SPARKS JA: Interstitial pneumonia with autoimmune features: aiming to define, refine, and treat. *Rev Colomb Reumatol* 2024; 31 (Suppl. 1): S45-S53. <https://doi.org/10.1016/j.rcreu.2023.07.006>
3. ACKMAN JB: Revisiting the diagnostic criteria for interstitial pneumonia with autoimmune features. *Radiology* 2025; 314: e250430. <https://doi.org/10.1148/radiol.250430>
4. PARK S, CHOE J, KIM HC, HWANG HJ, CHAE EJ, SEO JB: Evaluation of autoimmune features in patients with idiopathic pulmonary fibrosis and pathologic usual interstitial pneumonia: implications for CT patterns and prognosis. *Radiology* 2025; 314: e242292. <https://doi.org/10.1148/radiol.242292>
5. SERELIS J, ATHANASAKOS A, SKOPOULI FN, MOUTSOPOULOS HM: Interstitial lung pathology: should we test for autoantibodies to cellular antigens? *Clin Exp Rheumatol* 2019; 37: 340-14.
6. STEVENSON BR, THOMPSON GA, WATSON MC *et al.*: Autoantibodies in interstitial lung diseases. *Pathology* 2019; 51: 518-23. <https://doi.org/10.1016/j.pathol.2019.03.007>
7. ARBUCKLE MR, MCCLAIN MT, RUBERTONE MV *et al.*: Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med* 2003; 349: 1526-33. <https://doi.org/10.1056/nejmoa021933>
8. DEANE KD, HOLERS VM: Rheumatoid arthritis pathogenesis, prediction, and prevention: an emerging paradigm shift. *Arthritis Rheumatol* 2021; 73: 181-93. <https://doi.org/10.1002/art.41417>
9. ZAMPELI E, MAVROMMATI M, MOUTSOPOULOS HM, SKOPOULI FN: Anti-Ro52 and/or anti-Ro60 immune reactivity: autoantibody and disease associations. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): 134-41.
10. CAVAGNA L, TRALLERO-ARAGUÁS E, MELONI F *et al.*: Influence of antisynthetase antibodies specificities on antisynthetase syndrome clinical spectrum time course. *J Clin Med* 2019; 8: 2013. <https://doi.org/10.3390/jcm8112013>
11. CHAUDHRY S, CHRISTOPHER-STINE L: Myositis interstitial lung disease and autoantibodies. *Front Med (Lausanne)* 2023; 10: 1117071. <https://doi.org/10.3389/fmed.2023.1117071>
12. BETTERIDGE Z, MCHUGH N: Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. *J Intern Med* 2016; 280: 8-23. <https://doi.org/10.1111/joim.12451>
13. FENG F, WU Z, LI L *et al.*: Association between autoantibodies and interstitial lung disease in autoimmune disease patients: a retrospective study. *Clin Exp Rheumatol* 2026. <https://doi.org/10.55563/clineprheumatol/6r7qg8>
14. AVOUAC J, FRANSEN J, WALKER UA *et al.*: Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. *Ann Rheum Dis* 2011; 70: 476-81. <https://doi.org/10.1136/ard.2010.136929>
15. SEBASTIANI M, FAVERIO P, MANFREDI A *et al.*: Interstitial pneumonia with autoimmune features: why rheumatologist-pulmonologist collaboration is essential. *Biomedicines* 2021; 9: 17. <https://doi.org/10.3390/biomedicines9010017>
16. MIADLIKOWSKA E, MIŁKOWSKA-DYMANOWSKA J, BIAŁAS AJ *et al.*: Serum KL-6 and SP-D: markers of lung function in autoimmune-related interstitial lung diseases. *Int J Mol Sci* 2025; 26: 1091. <https://doi.org/10.3390/ijms26031091>
17. AXELSSON GT, GUDMUNDSSON G, PRATTE KA *et al.*: The proteomic profile of interstitial lung abnormalities. *Am J Respir Crit Care Med* 2022; 206: 337-46. <https://doi.org/10.1164/rccm.202110-2296oc>
18. PERELAS A, WINTER DL, SWIGRIS JJ, STREK ME, HIGHLAND KB: Interstitial pneumonia with autoimmune features: a literature review. *Respir Med* 2026; 252: 108641. <https://doi.org/10.1016/j.rmed.2026.108641>
19. WYGRECKA M, DZIEDZIC R: Beyond autoimmunity: rethinking progression in interstitial pneumonia with autoimmune features. *Pol Arch Intern Med* 2025; 135: 17144. <https://doi.org/10.20452/pamw.17144>
20. MIADLIKOWSKA E, MIŁKOWSKA-DYMANOWSKA J, BIAŁAS AJ *et al.*: Predictors of 1-year progression of interstitial lung disease in patients with interstitial pneumonia with autoimmune features: a single-center, prospective study. *Pol Arch Intern Med* 2025; 135: 17115. <https://doi.org/10.20452/pamw.17115>
21. OLDHAM JM, ADEGUNSOYE A, VALENZI E *et al.*: Characterisation of patients with interstitial pneumonia with autoimmune features. *Eur Respir J* 2016; 47: 1767-75. <https://doi.org/10.1183/13993003.01565-2015>
22. ENOMOTO N, YAZAWA S, MOCHIZUKA Y *et al.*: Radiological and histopathological features and treatment response by subtypes of interstitial pneumonia with autoimmune features: a prospective, multicentre cohort study. *Respir Med* 2024; 224: 107577. <https://doi.org/10.1016/j.rmed.2024.107577>
23. SAMBATARO G, SAMBATARO D, SPICUZZA L *et al.*: Progression and prognosis of intersti-

- tial pneumonia with autoimmune features: a longitudinal, prospective, multi-centre study. *Clin Exp Rheumatol* 2023; 41: 1140-48. <https://doi.org/10.55563/clinexprheumatol/lycdca>
24. LIBRA A, COLACI M, SPICUZZA L *et al.*: The pattern and progression of “usual” interstitial pneumonia with autoimmune features: comparison with patients with classic interstitial pneumonia with autoimmune features and idiopathic pulmonary fibrosis. *J Clin Med* 2024; 13: 369. <https://doi.org/10.3390/jcm13020369>
 25. JOERNS EK, GHEBRANIOUS MA, ADAMS TN, MAKRIIS UE: Evaluation of comorbidity burden on disease progression and mortality in patients with interstitial pneumonia with autoimmune features: a retrospective cohort study. *PLoS One* 2025; 20: e0316762. <https://doi.org/10.1371/journal.pone.0316762>
 26. UMASHANKAR E, ABDEL-SHAHEED C, PLIT M, GIRGIS L: Assessing the role for nail-fold videocapillaroscopy in interstitial lung disease classification: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2022; 61: 2221-34. <https://doi.org/10.1093/rheumatology/keab868>
 27. MCCOY SS, MUKADAM Z, MEYER KC *et al.*: Mycophenolate therapy in interstitial pneumonia with autoimmune features: a cohort study. *Ther Clin Risk Manag* 2018; 14: 2171-81. <https://doi.org/10.2147/tcrm.s173154>
 28. HUAPAYA JA, SILHAN L, PINAL-FERNANDEZ I *et al.*: Long-term treatment with azathioprine and mycophenolate mofetil for myositis-related interstitial lung disease. *Chest* 2019; 156: 896-906. <https://doi.org/10.1016/j.chest.2019.05.023>
 29. ZHAO Y, HUANG X, CAO X *et al.*: Efficacy and safety of tacrolimus in the treatment of interstitial pneumonia with autoimmune features: a retrospective study. *Front Pharmacol* 2025; 16: 1721639. <https://doi.org/10.3389/fphar.2025.1721639>
 30. MAHER TM, TUDOR VA, SAUNDERS P *et al.*: Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. *Lancet Respir Med* 2023; 11: 45-54. [https://doi.org/10.1016/s2213-2600\(22\)00359-9](https://doi.org/10.1016/s2213-2600(22)00359-9)
 31. D’SILVA KM, VENTURA IB, BOLSTER MB *et al.*: Rituximab for interstitial pneumonia with autoimmune features at two medical centres. *Rheumatol Adv Pract* 2021; 5 (Suppl. 2): ii1-ii9. <https://doi.org/10.1093/rap/rkab051>
 32. RAGHU G, REMY-JARDIN M, RICHELDI L *et al.*: Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022; 205: e18-e47. <https://doi.org/10.1164/rccm.202202-0399st>
 33. DISTLER O, HIGHLAND KB, GAHLEMANN M *et al.*: Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518-28. <https://doi.org/10.1056/nejmoa1903076>
 34. FLAHERTY KR, WELLS AU, COTTIN V *et al.*: Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718-27. <https://doi.org/10.1056/nejmoa1908681>