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REVIEW

Expert Perspectives: Defining and Managing Progressive Pulmonary Fibrosis in Systemic Sclerosis

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Systemic sclerosis–associated interstitial lung disease (SSc-ILD) is one of the leading causes of morbidity and mortality in SSc, affecting up to three-quarters of patients. The disease course is highly heterogeneous, ranging from indolent, nonprogressive forms to rapidly progressive pulmonary fibrosis (PPF). Identifying patients at risk for progression remains a key clinical challenge. Routine screening with high-resolution computed tomography at diagnosis and regular pulmonary function test monitoring are essential for early detection and timely management. Recent efforts have sought to harmonize the definition of PPF across fibrosing ILDs, recognizing shared clinical and pathophysiological mechanisms beyond idiopathic pulmonary fibrosis. Approximately 20% to 30% of patients with SSc-ILD develop PPF, yet reliable predictors of progression remain elusive. Advances in imaging, functional assessment, and molecular biomarkers hold promise for improving risk stratification. Therapeutic approaches have evolved from conventional immunosuppression toward combination and antifibrotic strategies. Mycophenolate mofetil remains the preferred first-line therapy, whereas nintedanib is the only antifibrotic agent approved for both SSc-ILD and PPF, having demonstrated efficacy in slowing lung function decline. Combination therapy, particularly mycophenolate mofetil with nintedanib or biologics such as rituximab and tocilizumab, is gaining traction in clinical practice despite limited comparative data. Emerging antifibrotic and anti-inflammatory agents offer new therapeutic prospects. This review summarizes current understanding of PPF in SSc-ILD, focusing on its evolving definition, prognostic determinants, and treatment landscape, and highlights unmet needs for personalized, evidence-based management.

CLINICAL CHALLENGE

The patient, a 40-year-old woman of Ivorian origin, presented with a one-year history of Raynaud phenomenon and progressive skin changes, including puffy hands evolving to diffuse skin sclerosis. Over the preceding six months, she developed exertional dyspnea (New York Heart Association [NYHA] class II), bilateral wrist and hands synovitis, and significant weight loss (6 kg). Laboratory evaluation revealed high-titer antinuclear antibodies (ANA; 1:2,500) with positive anti–topoisomerase I antibodies (ATA), raised C-reactive protein (CRP; 15 mg/L), and polyclonal hypergammaglobulinemia.

Pulmonary function tests (PFTs) showed severe restriction (predicted forced vital capacity [pFVC] 39% and predicted total lung capacity 52%) with markedly impaired gas exchange (diffusing capacity for carbon monoxide [DL_{CO}] unmeasurable), while echocardiography initially showed no sign of pulmonary hypertension (PH). Despite relatively preserved exercise tolerance, imaging and functional findings suggested mild interstitial lung disease (ILD) between 10% and 20% with a nonspecific interstitial

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pneumonia (NSIP) pattern. A diagnosis was made of NSIP in diffuse cutaneous systemic sclerosis (dcSSc).

She was treated with vasodilators (calcium-channel blocker), low-dose glucocorticoids, proton-pump inhibitors and methotrexate (MTX), switched after three months to mycophenolate mofetil (MMF) up to 3 g daily due to disease progression (both skin and lung). Over the next year, she experienced worsening respiratory symptoms (NYHA class III), declining functional capacity (pFVC 35%), and development of PH with right ventricular dilation. Further clinical deterioration led to discontinuation of MMF that was badly tolerated and initiation of rituximab combined with MTX.

Despite treatment escalation, her disease progressed with need for oxygen supplementation, thus requiring listing for lung transplantation. She underwent lung transplantation after continued functional decline, highlighting a rapidly progressive course of systemic sclerosis–associated ILD (SSc-ILD) with multiple risk factors for poor ILD prognosis.

BACKGROUND

SSc is a rare autoimmune disorder characterized by widespread fibrosis of the skin and internal organs, vascular abnormalities, and the presence of specific autoantibodies that vary by disease phenotype.[1] ILD is among the most common and serious complications of SSc, occurring in up to 75% of patients and contributing significantly to disease-related morbidity and mortality.

Alongside SSc in general, SSc- ILD presents a heterogeneous clinical course. Although some individuals experience a mild, nonprogressive form of ILD, others face rapid deterioration and severe pulmonary impairment. Therefore, regular surveillance of all patients is essential to detect early signs of progression and initiate timely interventions. Current evidence suggests that 20% to 30% of patients with SSc-ILD will develop progressive pulmonary fibrosis (PPF), whereas about half will remain stable or progress slowly, and a smaller proportion may even show improvement in lung function over time.[2] Accurately predicting which patients will follow a progressive course remains a major clinical hurdle, and managing progressive SSc-ILD remains difficult due to a limited number of high-quality trials.

This narrative review aims to provide a focused, clinically oriented synthesis of current evidence on PPF in SSc-ILD, emphasizing its conceptual evolution, prognostic implications, and therapeutic challenges rather than providing formal guideline recommendations.

APPROACH

Managing PPF in SSc-ILD requires a structured yet flexible approach that begins with establishing what progression is. The lack of a universally accepted definition, together with variability across existing criteria and their imperfect prognostic performance, represents a central clinical challenge that directly impacts patient identification and treatment decisions. Although international recommendations provide a framework for the management of SSc-ILD,[3,4] translating these into day-to-day clinical decisions requires a structured, stepwise approach.

In practice, treatment decisions should be guided by baseline disease severity, risk factors, and evidence of progression over time. In patients with limited ILD extent, no risk factors, and preserved lung function without evidence of progression, close monitoring every three to six months with PFTs and periodic imaging is appropriate. However, in patients with clinically significant ILD at baseline (eg, FVC <70% or more extensive fibrosis on imaging), presence of risk factors or those with objective decline in lung function, worsening respiratory symptoms, and evolution in high-resolution computed tomography (HRCT), treatment should be initiated or escalated without delay.

MMF is generally considered first-line therapy, particularly in patients with early or inflammatory disease. Cyclophosphamide, rituximab, or tocilizumab may be considered in selected cases (eg, rapidly progressive disease, early inflammatory phenotype, or intolerance to first-line therapy), although evidence and clinical practice vary.

In patients who exhibit disease progression despite adequate immunosuppression, or in whom the disease phenotype is predominantly fibrotic, initiation of antifibrotic therapy such as nintedanib or nerandomilast should be considered. In clinical practice, this often results in combination therapy (immunosuppressive plus antifibrotic), although high-quality evidence on optimal sequencing and combination strategies remains limited.

Importantly, treatment escalation should not be delayed until advanced functional decline occurs. Instead, early identification of progression and timely therapeutic intensification are critical because the greatest loss of lung function frequently, although not exclusively, occurs in the early phases of disease. Decisions should be individualized based on disease trajectory, radiologic pattern, extra-lung SSc-specific manifestations, comorbidities (including PH), and patient preferences. Within this framework, the identification of a progressive fibrosing phenotype serves as a practical trigger for treatment escalation, rather than solely a descriptive classification.

EVIDENCE

Definition of progression in SSc-ILD. PPF represents a concept within the spectrum of ILDs, characterized by a chronic, fibrosing phenotype that worsens over time, regardless of the underlying disease.[5] Indeed, fibrosing ILDs other than idiopathic PF (IPF), such as connective tissue disease (CTD)–associated ILDs, fibrotic hypersensitivity pneumonitis, idiopathic NSIP, unclassifiable ILDs, and others, can also behave with a progressive fibrotic trajectory akin to IPF. Identifying these conditions is clinically relevant because both functional decline and radiologic progression have been consistently associated with increased mortality in all fibrotic ILDs, including SSc-ILD.[6]

At present, there is no universally accepted definition of SSc-ILD progression. In 2018, Cottin et al first outlined criteria for defining PF-ILD, including a relative decline in FVC of ≥10%, a relative decline in DLco of ≥15%, or an FVC decline of 5% to 10% accompanied by worsening respiratory symptoms or radiographic changes within a two-year period.[7] The Outcome Measures in Rheumatology (OMERACT) initiative also proposed a definition of "clinically meaningful progression" in CTD-ILD, which applies to SSc-ILD. This definition mirrors that of Goh et al[8] and is based on PFT thresholds: a ≥10% relative decline in FVC or a 5% to 10% FVC decline paired with a ≥15% relative reduction in DLco over a 12-month period.[9]

The concept of progressive ILD gained further credibility through the INBUILD trial,[10] a pivotal study that evaluated the efficacy of nintedanib across diverse ILD subtypes. The INBUILD trial included various non-IPF–fibrosing ILDs with disease extents of ≥10% on HRCT at baseline and used broader criteria: a ≥10% relative decline in FVC, a 5% to 10% relative decline in FVC with either worsening symptoms or increased fibrosis on HRCT, or symptom worsening alongside radiologic progression, all within the previous 24 months.

More recently, the 2022 Clinical Practice Guideline by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) proposed a definition for PPF based on the occurrence of at least two of the following three criteria within one year: worsening respiratory symptoms, physiologic evidence of progression (including an absolute decline in FVC of ≥5% predicted and/or DLco decline of ≥10% predicted in the absence of another cause such as PH), and radiologic evidence of disease progression.[5] Compared to the INBUILD and OMERACT, the updated consensus introduces functional progression as an absolute (rather than relative) decline in lung function metrics over one year. It is important to emphasize that, in all definitions, PFT or HRCT changes are assessed within a 12- or 24-month window. This does not mean that patients must wait the full period to be classified as progressors; rather, if qualifying changes occur at any point within this timeframe, the patient can be appropriately classified as having disease progression. A comparison of the main criteria used to define progressive ILD, and their respective studies, is provided in Table 1.

Prevalence of progression in SSc-ILD. The prevalence of progression in SSc-ILD varies widely depending on the definition applied and the population studied.[11] In cohorts including all patients with SSc, estimates of ILD progression range broadly,

Table 1. Key definitions of progression in SSc-ILD*

Criteria or definition	Key components	Timeframe	Notes	References
ATS/ERS/JRS/ALAT 2022 (official PPF criteria)	≥2 of the following: • Worsening respiratory symptoms • Absolute decline in FVC ≥5% • Radiologic progression (HRCT)	Within 12 mo	Most recent criteria; awaits validation in SSc-ILD	Raghu et al[5]
PF-ILD criteria (INBUILD criteria)	• Relative decline in FVC ≥10% predicted or • Relative decline in FVC ≥5% to <10% predicted and worsened respiratory symptoms or • Relative decline in FVC ≥5% to <10% predicted and increased extent of fibrosis on HRCT or • Worsened respiratory symptoms and increased extent of fibrosis on HRCT	Within 24 mo	Broader than ATS definition; used to select patients for INBUILD trial and the FIBRONEER-ILD trial	Flaherty et al[10]
OMERACT criteria	• Relative decline in FVC ≥10% predicted or • Relative decline in FVC ≥5% to <10% predicted with a ≥15% relative decline in DLco	12 mo		Khanna et al[9]
EUSTAR criteria	• Absolute decline in FVC ≥10% predicted or • Absolute decline in FVC ≥5% to <10% predicted with a ≥15% absolute decline in DLco	12 mo		De Lorenzis et al[11]
FVC decline alone	Absolute decline in FVC ≥5% or ≥10%	6–24 mo	Common in earlier studies before composite criteria were introduced	

* ALAT, Latin American Thoracic Association; ATS, American Thoracic Society; DLco, diffusing capacity for carbon monoxide; ERS, European Respiratory Society; EUSTAR, European Scleroderma Trials and Research; FVC, forced vital capacity; HRCT, high-resolution computed tomography; JRS, Japanese Respiratory Society; PPF, progressive pulmonary fibrosis; SSc-ILD, systemic sclerosis–associated interstitial lung disease; OMERACT, Outcome Measures in Rheumatology.

reflecting differences in ILD ascertainment and follow-up. When analyses are restricted to patients with established SSc-ILD, more consistent estimates emerge, typically ranging from approximately 20% to 40% over one to two years.

For example, analyses from Scleroderma Lung Study II and European cohorts report progression rates around 19% to 30%,[12,13] whereas higher estimates (up to approximately 40%) have been observed in incident or early ILD cohorts using ATS 2022 criteria.[14,15] Importantly, direct comparisons across studies remain challenging due to heterogeneity in PPF definitions, inclusion criteria, and follow-up duration (Figure 1).

Indeed, the patterns of SSc-ILD progression are highly variable, making it difficult to identify which patients are at greatest risk and to determine the optimal timing for therapeutic intervention. In a landmark study,[2] Hoffmann-Vold et al examined disease progression in 826 patients with SSc-ILD from the European Scleroderma Trials and Research (EUSTAR) database. Within a 12 ± 3-month period, 27% developed progressive ILD, defined by either a moderate FVC decline (between 5% and 10%) or a marked decline (>10%). Across any given 12-month interval, 23% to 27% of patients with SSc-ILD demonstrated progression; however, only a small subset experienced progression over consecutive periods. The most frequent progression pattern, observed in 58% of progressive cases, involved a slow functional decline interspersed with periods of stability or improvement. In contrast, approximately 8% of patients exhibited a more aggressive course, characterized by a steady and rapid FVC decline. Overall, approximately 67% of patients with SSc-ILD experienced disease progression at some point during an average follow-up period of five years. In another recent study,[6] 25% to 30% of patients with SSc-ILD could be classified as progressors at each 12-month follow-up, according to different definitions, but only a

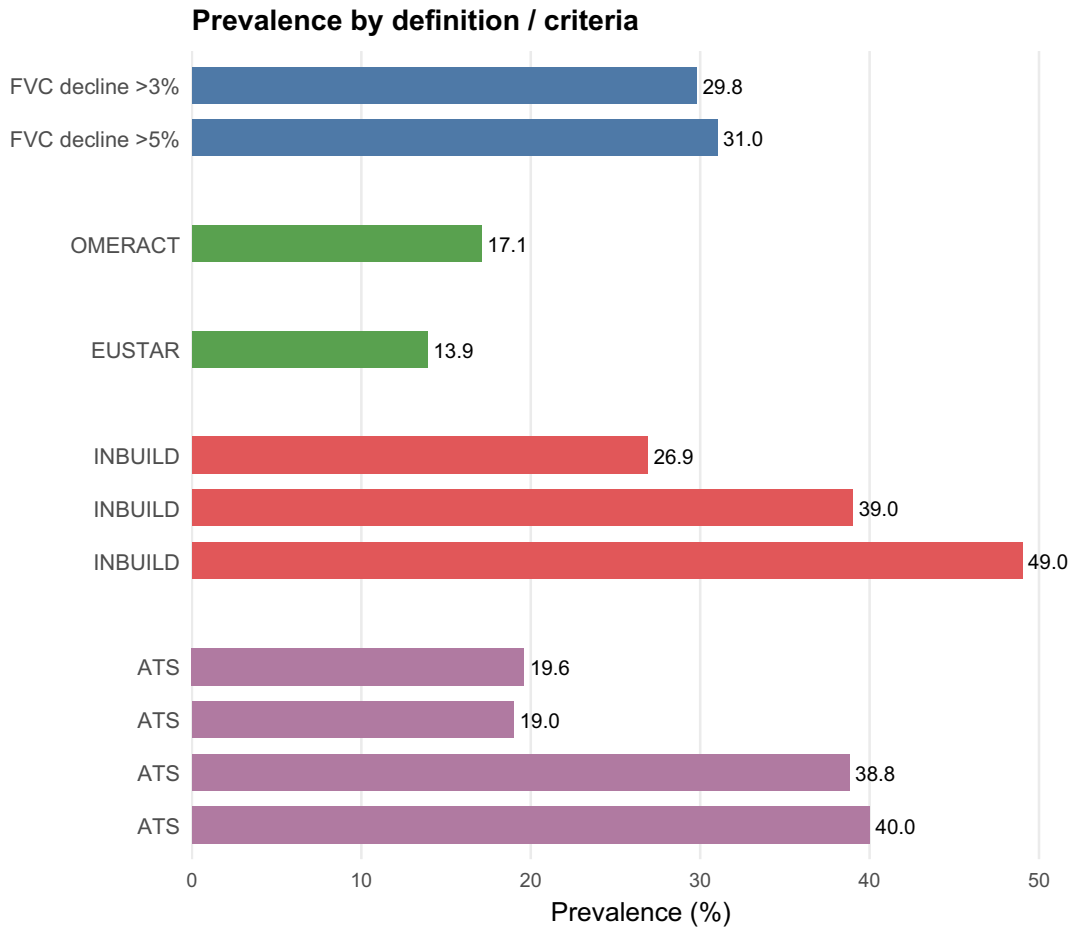

Figure 1. Prevalence of progressive phenotype in SSc-ILD across studies and definitions. Horizontal bar chart comparing the proportion of patients with SSc-ILD meeting various definitions of progression. Definitions include relative FVC decline thresholds (>3% and >5%), progression criteria used in OMERACT and EUSTAR cohorts, and multiple progression definitions applied in the INBUILD trial. Prevalence estimates based on ATS/ERS/JRS/ALAT clinical practice guideline criteria are also shown. Together, the data highlight substantial variability in the proportion of patients with SSc-ILD classified as progressive depending on the assessment framework applied. ALAT, Latin American Thoracic Association; ATS, American Thoracic Society; ERS, European Respiratory Society; EUSTAR, European Scleroderma Trials and Research; FVC, forced vital capacity; JRS, Japanese Respiratory Society; SSc-ILD, systemic sclerosis–associated interstitial lung disease; OMERACT, Outcome Measures in Rheumatology.

minority of patients showed progression in consecutive periods, and, importantly, ILD progression at the first follow-up reduced the risk for subsequent progression. These observations should be interpreted with caution, however, because they may be influenced by regression to the mean and by a threshold effect.

Prognosis of progressive SSc-ILD. ILD has been the leading cause of mortality in SSc for several decades, consistently accounting for a substantial proportion of SSc-related deaths, as observed for example in the largest worldwide registry (EUSTAR).[16] Patients with SSc who have ILD at diagnosis, even when mild and with FVC within the normal ranges, have reduced survival.[17] Declines in lung function over 12 months, particularly in %pFVC or %pDLco, have consistently been linked to poorer survival outcomes.[18] Notably, even a single episode of ≥5% FVC decline is significantly associated with increased mortality after adjusting for other risk factors.[6,18]

Early lung function decline thus serves both as a marker of disease progression and as a potential surrogate endpoint for clinical trials and treatment decisions. However, relying solely on PFTs may overlook patients with preserved lung volumes but worsening radiographic or symptomatic profiles, highlighting the need for multidimensional assessment strategies such as PF-ILD and PPF definitions.

The prognostic value of guideline PPF criteria remains uncertain so far in SSc-ILD, although it has been confirmed in nonfibrotic ILDs.[19] In an incident SSc-ILD cohort, applying PPF criteria was independently associated with a 2.6-fold higher mortality.[14] However, in a prevalent SSc-ILD cohort, fulfilling PPF criteria did not significantly predict long-term mortality, unlike other definitions such as Goh staging,[8] INBUILD criteria, or ≥5% FVC decline.[15] These findings suggest that PPF criteria may be less effective in identifying high-risk patients than less stringent definitions of progression.

Screening and monitoring SSc-ILD progression. Early detection of ILD in SSc is critical because significant lung involvement can severely impair quality of life. Screening typically combines symptom assessment, chest auscultation, PFTs, and HRCT.[9,20] Because ILD may be present even without symptoms or PFT abnormalities, reliance on PFT alone is problematic, though it remains central to longitudinal monitoring.[21] HRCT is more sensitive and considered the diagnostic gold standard, but practices for its use vary widely worldwide.[22]

Recently, international guidelines from both the ERS/EULAR task force and the American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) collaboration have provided updated, evidence-based recommendations on screening and monitoring for SSc-ILD.[4,23] Both documents converge on the central role of HRCT and PFTs as the cornerstone of baseline evaluation. Despite low-quality evidence, both major guidelines support HRCT screening, albeit ERS/EULAR recommend screening all patients with SSc, regardless of additional risk factors, whereas ACR/CHEST suggest screening only CTD patients at higher risk. Regarding monitoring, both guidelines support regular PFTs and HRCT, though the intensity differs. Table 2 summarizes similarities and differences between the two guidelines.

Quantitative HRCT and artificial intelligence–assisted imaging approaches are emerging as objective tools to improve detection, risk stratification, and monitoring of SSc-ILD progression, offering greater reproducibility and sensitivity to subtle changes compared with visual assessment.[24] In parallel, novel imaging modalities, including photon-counting CT, lung magnetic resonance imaging, and molecular techniques such as fibroblast activation protein inhibitor–positron emission tomography/CT, may further enhance early detection and provide insight into active fibrotic processes.[25] However, these technologies remain investigational, and their integration into routine clinical practice requires further validation and standardization.

Risk factors for SSc-ILD progression. Recognized risk factors for ILD onset in SSc include male sex, non-White ethnicity, diffuse cutaneous involvement, ATAs, absence of anticentromere antibodies, and elevated inflammatory markers.[26] Importantly, many of these features also translate into predictors of progression (Figure 2 and Table 3).

Among demographic factors, male sex is the most consistent, conferring an approximately three-fold higher risk of developing PPF,[2,13,27,28] whereas older age is more strongly linked to mortality than to progression itself.[14,17,29] African American patients with SSc consistently exhibit more severe ILD and develop lung involvement at an earlier age compared to Caucasian patients, as demonstrated across multiple cohorts. This represents an important and well-established risk factor for worse outcomes.[30]

Disease-specific features play a central role in shaping disease trajectory: ATA positivity is strongly associated with ILD onset and progression across cohorts, with an estimated approximately 50% increased risk of PPF,[14,31,32] whereas anti-Ro52 antibodies have been linked to greater disease severity.[33] Other autoantibodies, including antifibrillarin, anti-Th/To, and Anti-PM/Scl, have also been associated with ILD and should be considered in risk stratification. Diffuse cutaneous involvement and higher modified Rodnan skin Score without thickness consistently predict functional decline, likely reflecting a greater systemic fibrotic and inflammatory burden.[2,14,32] Importantly, although diffuse cutaneous disease confers the highest risk, patients with limited cutaneous SSc—particularly those with high-risk autoantibody profiles—may also experience significant progression. In contrast, anticentromere antibodies are generally associated with a lower risk of progressive ILD. Disease duration is a well-established determinant of progression risk, with the highest rates of ILD progression observed in early disease. Although progression can occur later, particularly in fluctuating or relapsing

Table 2. Comparison of ERS/EULAR and ACR/CHEST guidelines for SSc-ILD screening and monitoring*

Topic	ACR/CHEST 2023	ERS/EULAR 2025	Similarities	Main differences
Who to screen	Conditional recommendation for PFTs and HRCT for patients with SSc at risk.	Strong recommendation to systematically screen all patients with SSc with HRCT (ie, independent of additional risk factors).	Both recommend active screening in SSc.	ERS/EULAR: screen all patients with SSc with HRCT. ACR/CHEST uses a conditional approach (screen patients with SSc with risk factors).
Screening	Conditionally recommend baseline PFTs and HRCT chest for screening of at-risk SSc. Conditionally recommend against screening with chest radiograph and 6MWD; recommend against surgical lung biopsy for screening.	Strong recommendation to use HRCT as the primary screening tool (do not replace HRCT with PFTs/US). PFTs (FVC/DLco) are recommended as complementary assessments, especially if HRCT or symptoms are present. ERS/EULAR also supports use of 6MWT and PROMs for assessment of severity or prognosis in appropriate patients.	Both recognize HRCT and PFTs as the key tests. Both discourage chest x-ray or surgical lung biopsy for routine screening.	ERS/EULAR gives stronger language in favor of HRCT as the main screening test for SSc; ACR phrases HRCT plus PFTs as conditional recommendations.
Monitoring	Conditionally recommend monitoring with PFTs, HRCT chest, and ambulatory desaturation testing; conditionally recommend against routine 6MWD and chest radiography for monitoring. The guideline provides suggested monitoring intervals (adapted to disease and risk).	Conditionally recommend regular PFT monitoring and suggest repeating HRCT at intervals stratified by risk (every 12 mo in high-risk patients <5 y of disease duration).PFT frequency is suggested (eg, repeat every 3–6 mo during early or unstable period and at least every 6–12 mo thereafter) with stratification by risk. 6MWT and PROMs can be used for severity or prognosis.	Both support longitudinal monitoring with PFTs and HRCT (and acknowledge ambulatory/exercise testing has a role).Both stress individualized intervals based on risk.	ERS/EULAR gives more concrete interval suggestions (PFT every 3–6 mo initially, then every 6–12 mo; HRCT every 1–2 y in SSc unless change suspected).ACR/CHEST is more conservative/ conditional but offers suggested intervals for patients with SSc (eg, PFTs every 3–6 mo initially, ambulatory desaturation every 3–12 mo as needed).
Monitoring triggers (when to repeat HRCT or investigate for progression)	Suggest repeating tests when there is clinical concern or change (decline in PFTs, new or worsening symptoms, and desaturation), and guidance gives context-specific suggestions; conditional recommendation for added ambulatory desaturation in monitoring.	ERS/EULAR recommends repeating HRCT and PFTs if progression suspected, provides risk stratification to decide monitoring frequency, and suggests earlier imaging for high-risk or rapidly changing patients.	Both use clinical change (symptoms, PFT decline, and desaturation) as trigger for intensified monitoring or repeat HRCT.	ERS/EULAR gives more formal risk stratification tools or algorithms and explicit recommended intervals for repeat imaging in SSc. ACR emphasizes clinical judgement and provides conditional/ suggested intervals.

* 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ACR, American College of Rheumatology; CHEST, American College of Chest Physicians; DLco, diffusing capacity for carbon monoxide; ERS, European Respiratory Society; FVC, forced vital capacity; HRCT, high-resolution computed tomography; PFT, pulmonary function test; PROM, patient-reported outcome measure; SSc-ILD, systemic sclerosis–associated interstitial lung disease; US, ultrasound.

patterns, the emphasis of clinical trials on early SSc reflects the consistent observation that the initial disease phase carries the greatest risk.[31,32,34]

Comorbidities and systemic features may further modulate risk: gastroesophageal reflux disease has been associated with a modest increase in progression risk,[2,13,35] although its independence from other disease manifestations remains uncertain, whereas elevated inflammatory markers such as CRP and interleukin-6 correlate with worse lung function and outcomes but show limited value as independent predictors of PPF.[14,28,36–38] Additional clinical features incorporated into composite models, such as arthritis and exercise-induced desaturation, may improve early identification of patients at risk of rapid progression.[39]

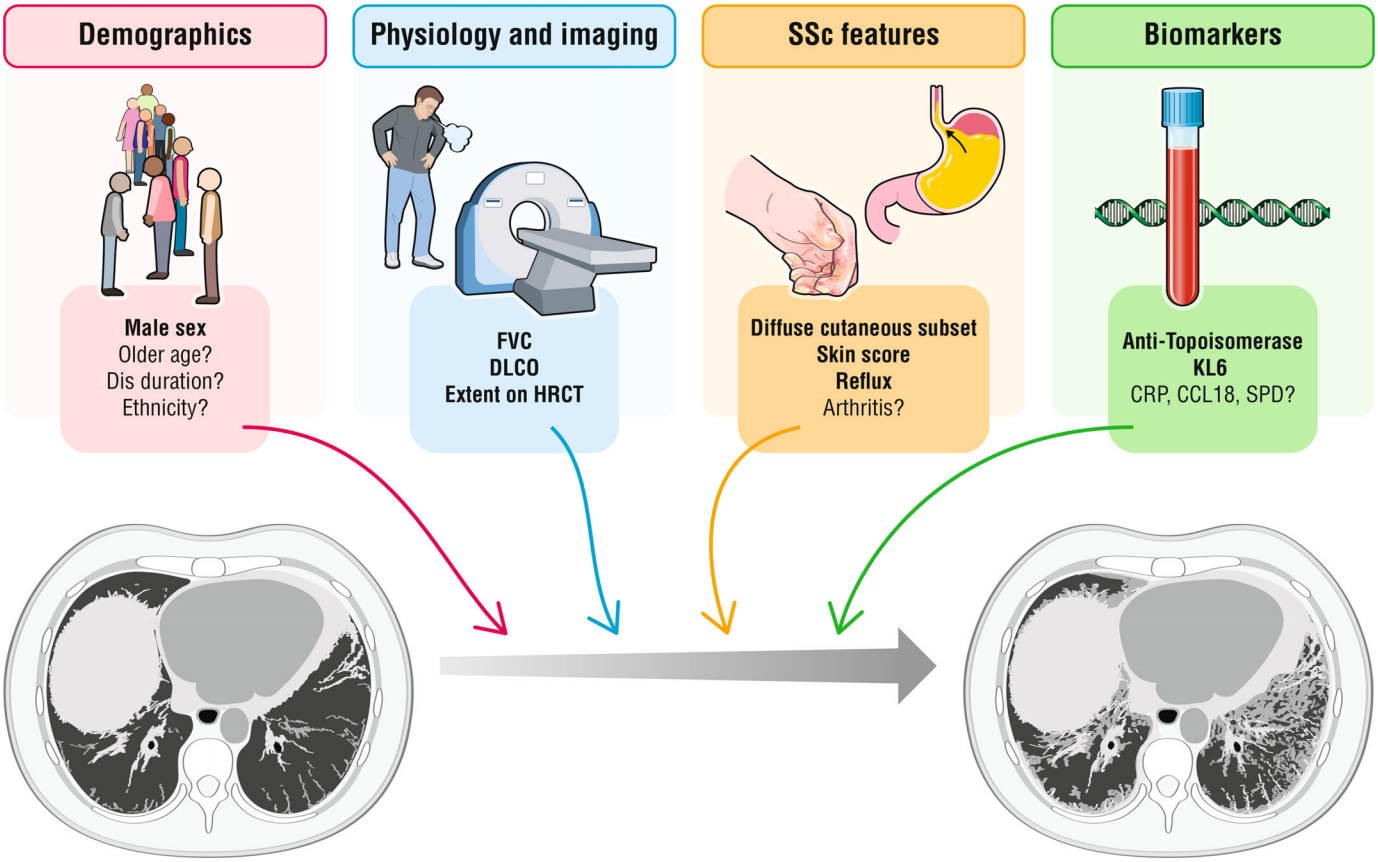

Figure 2. Predictors of progression in SSc-ILD. Schematic overview of key clinical domains and variables associated with progression of ILD in SSc. These include demographics (male sex, potential associations with older age, longer disease duration, and ethnicity), physiology and imaging findings (reduced FVC, impaired DLco, and greater fibrosis extent on HRCT), SSc-related features (diffuse cutaneous subtype, higher skin score, presence of gastroesophageal reflux, and possibly arthritis), and biomarkers (anti–topoisomerase I antibodies and KL-6, with emerging roles for CRP, CCL18, and SP-D). These factors may contribute to worsening fibrosis over time, illustrated by progression from earlier to more advanced radiographic involvement. CCL, chemokine (C-C motif) ligand; CRP, C-reactive protein; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; KL-6, Krebs von den Lungen 6; SP-D, surfactant protein-D; SSc-ILD, systemic sclerosis–associated interstitial lung disease.

Among lung-specific factors, the extent of fibrosis on HRCT appears to be more strongly associated with disease progression and mortality than radiologic pattern alone,[8,31,40–42] despite the predominance of fibrotic NSIP and the presence of usual interstitial pneumonia–like features in a subset of patients[43,44]; however, the independent predictive value of fibrosis extent has not been consistent across studies. Lower baseline FVC is associated with an increased risk of progression,[28,31,45] whereas reduced DL_{CO} is a more robust predictor of overall mortality than progression,[42] and importantly, short-term declines in FVC and DLco over the first one to two years are stronger indicators of long-term outcomes than baseline values alone.[29] Importantly, reduced DLco requires careful interpretation in SSc due to the frequent coexistence of pulmonary vascular disease.

Biomarkers and prediction of SSc-ILD progression. Despite these associations, prediction of progression at the individual patient level remains challenging. Several multivariable models incorporating demographic, clinical, functional, and serologic variables have been proposed,[12,32,46] but their performance is modest (typically area under the curve of approximately 0.60–0.70), they lack external validation, and even machine learning approaches applied to large cohorts have not substantially improved predictive accuracy,[47] highlighting the limitations of routinely collected clinical data.

Similarly, although numerous circulating biomarkers have been investigated, none have yet been validated for routine clinical use. Krebs von den Lungen 6 (KL-6), surfactant protein-D, and chemokine (C-C motif) ligand 18 (CCL18) consistently correlate with ILD presence, severity, and functional impairment,[48] with KL-6 and CCL18 also showing prognostic associations with progression and mortality,[49–52] whereas dynamic changes in KL-6 may reflect treatment response. Chemokine (C-X-C motif) ligand 4 has been associated with increased risk of PPF and may also identify patients more likely to respond to immunosuppressive therapy,[13] whereas elevated CCL18 is linked to faster functional

Table 3. Risk factors and predictors of progression in SSc-ILD*

Category	Biomarker or risk factor	Associated with	Notes
Autoantibodies	Anti–topoisomerase I	Presence and progression	Strongly associated with SSc-ILD, especially in diffuse cutaneous SSc
	Anti-CXCR3 or anti-CXCR4	Progression	Higher levels in SSc-ILD; low levels may indicate faster progression
Inflammatory markers	IL-6 and CRP	Progression and mortality	Elevated levels linked to worse outcomes
	CCL18	FVC decline, progression, and mortality	Strong prognostic biomarker
	CCL2 and CXCL4	Progression	Suggest fibrotic activity and immune activation
Lung-specific proteins	KL-6 and SP-D	Lung damage and FVC decline	Higher levels linked to advanced ILD
Demographics	Male sex and African American ethnicity	Presence and worse prognosis	Higher prevalence and mortality risk
	Older age	Mortality	Age is an independent risk factor
Clinical indicators	Diffuse cutaneous SSc	Presence and progression	More severe disease phenotype
	Low baseline FVC or DL_{CO}	Progression and mortality	Predictive of long-term outcomes
	Extensive disease on HRCT	Progression	>20% Extent increases risk 3-fold
	History of arthritis and low SpO_2 (SPAR model)	Progression of mild ILD	Predictive score for early progression

* CCL, chemokine (C-C motif) ligand; CRP, C-reactive protein; CXCL, chemokine (C-X-C motif) ligand; CXCR, chemokine (C-X-C motif) receptor; DL_{CO}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL-6, interleukin-6; KL-6, Krebs von den Lungen 6; SPAR, SpO_2 and arthritis; SP-D, surfactant protein-D; SSc-ILD, systemic sclerosis–associated interstitial lung disease.

decline and poorer survival, particularly in early disease.[53,54] Other candidates, such as anti–chemokine (C-X-C motif) receptor 3 and 4 antibodies, show differential expression in patients with progressive versus stable disease, but their clinical applicability remains uncertain.[55] A more recent study has shown that high serum type I interferon score is associated with worse lung involvement and poorer longitudinal outcomes in patients with dcSSc.[56] Overall, although multiple demographic, disease-specific, functional, and molecular factors contribute to the risk of progression, their limited predictive performance reinforces the need for integrated, longitudinal assessment strategies rather than reliance on single markers.

Initial management of SSc-ILD. Treatment options for SSc-ILD have expanded significantly in recent years, with immunosuppressants and antifibrotics forming the cornerstone of current management. The decision to treat or not to treat patients with SSc-ILD is usually based on patient characteristics and risk factors for severe disease. Given the multisystemic nature of SSc, some patients with lung involvement may receive immunosuppressive therapy primarily for other organ manifestations, which nonetheless impacts on ILD progression and response. Of note, patients with SSc-ILD left untreated may experience disease progression in up to 40% of cases, as much as patients receiving immunosuppressive therapy.[57] Earlier intervention may prevent clinical worsening and progressive ILD in patients with early SSc,[58] although in a real-life study, earlier initiation of immunosuppressive therapy did not prevent the onset of ILD.[59] However, interpretation of these findings is limited by the high proportion of patients receiving MTX, which has not been shown to be effective for SSc-ILD.

MMF is considered the cornerstone of treatment for SSc-ILD, supported by evidence from a randomized controlled trial demonstrating a comparable efficacy to cyclophosphamide in stabilizing lung function with better tolerability.[60] MMF use improves disease progression and quality-of-life measures as reported by several real-life studies.[61] As such, MMF is the first-line therapy for most patients with mild to moderate ILD and is often maintained long-term due to its favorable safety profile. The use of MMF in SSc-ILD has been recommended by consensus panels[20] and in recently issued treatment guidelines.[3,4,62]

Alternatives to MMF include rituximab and tocilizumab, both of which have shown promise in SSc-ILD.[63,64] Rituximab, targeting CD20+ B cells, has demonstrated stabilization or improvement in lung function in small trials and was noninferior to cyclophosphamide in the RECITAL study, targeting patients with severe CTD-ILD, with a better safety profile.[65] It also improved FVC in the DESIRES trial,[66] particularly in patients with elevated CRP, offering steroid-sparing benefits. Tocilizumab, an anti–IL-6 receptor antibody, slowed FVC decline in the faSSci-nate and focuSSced trials,[67] with possibly greater benefit in ATA-positive patients. It has also been associated with improved imaging findings, reduced skin involvement and favorable long-term safety.[68] Importantly, these trials were conducted in patients with early disease, and there is currently limited evidence supporting the use of tocilizumab in advanced or refractory SSc-ILD. Based on these data, tocilizumab is Food and Drug Administration (FDA)–approved for SSc-ILD, whereas rituximab remains widely used off-label, particularly in refractory or overlapping cases.

Despite the lack of head-to-head studies, real-world data from the EUSTAR registry[69] suggest comparable effectiveness among MMF, tocilizumab, rituximab, and cyclophosphamide. Similarly, in selected expert surveys, some clinicians have perceived safety profiles as equivalent and efficacy as highest for rituximab and nintedanib.[70] Consequently, the recent ERS/EULAR recommendations[4] remain guided by trial inclusion criteria rather than direct comparative evidence, highlighting the need for more pragmatic studies.

Although immunosuppressive agents remain central to SSc-ILD management, antifibrotic therapy represents a complementary approach. Nintedanib is an approved antifibrotic for both SSc-ILD and PPF, supported by the SENSCIS[71] and INBUILD[10] trials. Importantly, SENSCIS evaluated nintedanib in a broad SSc-ILD population not enriched for progressive disease, demonstrating a reduction in FVC decline over 52 weeks, including in patients receiving background immunosuppressive therapy. Diarrhea is the most common adverse event and is often manageable; however, in the SENSCIS trial, approximately 17% of patients discontinued treatment due to adverse events.

Real-world data from the EUSTAR registry show a substantial shift in SSc-ILD treatment strategies over time, with increased use of immunosuppressive and combination therapies accompanied by a decline in progression rates.[72] However, a significant proportion of patients continue to progress despite these advances, underscoring the need for more effective and individualized therapeutic approaches.

Management of progressive SSc-ILD. For patients with progressive SSc-ILD, the strongest evidence for antifibrotic therapy comes from the INBUILD trial,[10] which enrolled patients with progressive fibrosing ILDs, including SSc-ILD, and demonstrated a significant reduction in the rate of FVC decline with nintedanib compared with placebo. Although observational and real-world studies are limited in their ability to establish efficacy, their findings are consistent with trial results with regard to FVC trajectory, tolerability of the drug and lack of effects on other aspects of the disease.[73]

In current clinical practice, nintedanib is frequently positioned as a second-line agent in patients who exhibit disease progression despite immunosuppressive therapy; however, progression is not a prerequisite for its efficacy. Yet the SENSCIS trial clearly demonstrated that nintedanib significantly reduced the rate of FVC decline compared to placebo even in patients with relatively stable disease who had ≥10% ILD extent on HRCT, supporting its use not only in progressive cases but also as an early intervention regardless of baseline disease activity. This is also underlined in the recent ERS/EULAR guidelines that suggest upfront combination therapy with MMF and nintedanib in patients with a high risk of progression.[4]

Given its antifibrotic properties and established efficacy in IPF, pirfenidone has also been explored as a potential alternative to nintedanib in the treatment of progressive SSc-ILD. The LOTUSS study, an open-label 16-week trial investigating the safety and tolerability of pirfenidone in patients with SSc-ILD, demonstrated an acceptable safety profile. However, the Scleroderma Lung Study III, which assessed MMF in combination with either placebo or pirfenidone, showed no significant difference in %pFVC at 18 months between the two arms.[74] The study was, however, believed to be underpowered to detect treatment differences.

Phosphodiesterase 4 (PDE4) inhibition, already established in the treatment of inflammatory diseases, has recently gained attention for its antifibrotic potential. By preventing the breakdown of cyclic adenosine monophosphate, PDE4 inhibitors enhance signaling pathways involving prostaglandin E2, prostacyclin, and adenosine, which contribute to the inhibition of fibroblast activation and promotion of epithelial repair.

Nerandomilast (formerly BI 1015550) is a preferential PDE4B small-molecule inhibitor developed to deliver antifibrotic and anti-inflammatory effects while improving tolerability over traditional pan-PDE4 inhibitors. Preclinical studies showed that nerandomilast reduces fibrotic markers, suppresses fibroblast-to-myofibroblast differentiation, and improves endothelial barrier integrity. It also modulates key pathways such as MAPK and transforming growth factor β, supporting its potential as a disease-modifying therapy in fibrotic ILDs.

In a Phase II trial involving patients with IPF, nerandomilast (18 mg bis in die [BID]) stabilized FVC over 12 weeks, regardless of background antifibrotic use. Post hoc analysis suggested an additive effect when used with nintedanib. These promising results led to two large Phase III trials: FIBRONEER-IPF[75] and FIBRONEER-ILD,[76] which evaluated nerandomilast in IPF and PPF, respectively. Both trials demonstrated statistically significant reductions in FVC decline at 52 weeks for nerandomilast (9 and 18 mg BID) compared to placebo. In FIBRONEER-IPF, the treatment-placebo difference was +68.8 mL for the 18-mg dose. FIBRONEER-ILD similarly showed reductions of +67.2 mL and +81.1 mL for the 18-mg and 9-mg groups, respectively. Importantly, nerandomilast also demonstrated a significant reduction in mortality in the PPF trial, with hazard ratios of 0.48 (18 mg) and 0.60 (9 mg) compared to placebo. Diarrhea was the most frequent adverse event, particularly at the higher dose (41.3% vs 16.0% for placebo), but was generally manageable. No increased risk of psychiatric or vasculitic events was observed. Based on these data, nerandomilast has recently been approved by the FDA for the treatment of PPF. Ongoing clinical trials are now evaluating its role specifically in SSc-ILD and SSc more broadly.

The role of combination therapy. Combination therapy is gaining prominence in the management of SSc-ILD, reflecting the disease's dual pathogenesis of immune-mediated inflammation and progressive fibrosis. Although monotherapy remains the

standard first-line approach,[62] many patients continue to progress. In the SENSCIS trial, nintedanib significantly reduced FVC decline in patients receiving background immunosuppression with MMF, and post hoc analyses confirmed the safety and potential additive benefit of this regimen.[77] Increasing attention is also directed toward combining MMF or other immunosuppressants with biologic agents such as rituximab, particularly in refractory disease or overlapping autoimmune phenotypes. Although early data[78] and recent ERS/EULAR guidance[4] support such strategies in patients at high risk of progression, robust trial evidence remains limited. Nevertheless, expert surveys and registry studies indicate that combination therapy is already widely adopted in clinical practice,[70,72] especially for nintedanib and rituximab.

Treatment of refractory SSc-ILD and investigational agents. In patients with rapidly progressive or refractory disease, additional or alternative therapeutic strategies may be required. Hematopoietic stem cell transplantation has shown significant long-term benefits in selected patients, including improved event-free survival and pulmonary outcomes, although at the cost of early treatment-related morbidity and mortality. Chimeric antigen receptor T cell therapy is an emerging investigational approach, showing early promise in refractory autoimmune diseases, including SSc-ILD, by selectively depleting autoreactive B cells.[79] Recent early-phase data suggest that other B cell–targeting strategies, such as bispecific T cell engagers, may achieve clinical improvement and stabilization of ILD even in patients with treatment-refractory SSc.[80] However, these approaches remain experimental and are associated with significant safety considerations, highlighting both the therapeutic potential and current limitations of next-generation immune therapies. In cases of end-stage lung disease or PPF despite maximal medical therapy, lung transplantation may be considered.[4]

Several repurposed or novel therapeutic agents are currently under active investigation for the treatment of PPF (Table 4). These include antifibrotic, anti-inflammatory, and immunomodulatory compounds aimed at halting or reversing fibrotic progression across various ILD subtypes. Tyrosine kinase inhibitors beyond nintedanib, hedgehog pathway inhibitors, and angiotensin II type 2 receptor agonists have advanced into Phase II or III trials.[81] Inhaled treprostinil, which targets vascular and fibrotic pathways, has demonstrated efficacy in IPF and is also being explored in PPF. Although most trials to date have focused on IPF, PPF as a group, or unclassifiable fibrosis, the mechanistic overlap between the various fibrotic ILDs suggests that select agents may eventually benefit patients with SSc-ILD exhibiting a progressive phenotype.

DISCUSSION

There is growing recognition that a subset of patients with SSc-ILD develops a progressive fibrosing phenotype with important prognostic implications. However, the clinical utility of the PPF construct in SSc remains to be fully established, and its role in guiding management decisions continues to evolve. This evolving recognition is shaping more tailored surveillance strategies, with HRCT at baseline and pulmonary function monitoring playing complementary roles in initial evaluation and long-term follow-up. Importantly, predicting disease trajectory remains difficult because of the heterogeneity of SSc-ILD and the limitations of current biomarkers and clinical models. Despite these challenges, important advances are being made, with the approval of novel antifibrotic therapies marking a new era in PPF treatment.

Going forward, more SSc-specific prospective data are needed to better characterize progression, refine risk stratification tools, and validate emerging therapies. In this context, several key challenges continue to hinder progress in the field.

Table 4. Ongoing clinical trials in PPF*

Treatment class	Molecule	Trial name or ClinicalTrials.gov ID	Phase or type	Status	Duration; N Patients	Primary endpoint
Antifibrotic	Inhaled pirfenidone	NCT06329401	Phase 2b, DBPC, randomized	Recruiting	52 wk; 300	Change from baseline in FVC
	HEC585 (yinfenidone)	NCT05139719	Phase 2b, DBPC, randomized	Recruiting	24 wk; 110	Change from baseline in FVC
LPA1 antagonist	Admilparant	NCT06003426	Phase 3, DBPC, randomized	Recruiting	52 wk; 1,185	Absolute FVC change; syncopal events
	Admilparant	ALOFT; NCT06025578	Phase 3, DBPC, randomized	Recruiting	52 wk; 1,092	Absolute FVC change; syncopal events
Prostacyclin agonist	Inhaled treprostinil	TETON-PPF; NCT05943535	Phase 3, DBPC, randomized	Recruiting	52 wk; 698	Absolute change from baseline in FVC
Hedgehog inhibitor	Taladegib (ENV-101)	WHISTLE-PF; NCT06422884	Phase 2b, DBPC, randomized	Not yet recruiting	24 wk; 320	Safety
Tyrosine kinase inhibitor	Anlotinib	NCT05828953	Phase 2–3, DBPC, randomized	Recruiting	52 wk; 30	Absolute change from baseline in FVC

* DBPC, double-blind placebo-controlled; FVC, forced vital capacity; LPA1, lysophosphatidic acid receptor 1; PPF, progressive pulmonary fibrosis.

A key unmet need in SSc-ILD is accurately identifying which patients are likely to experience disease progression. Despite advances in imaging, PFT, and biomarker research, predicting which individual patients will progress in a timeframe of one to three years remains a challenge. These limitations not only hinder timely intervention but also complicate clinical trial design because enrolling a heterogeneous population dilutes the ability to detect treatment effects.

Another major unanswered question is why some patients with SSc-ILD develop PPF while others remain stable for years. The simple "progressive versus stable" model is being reconsidered because many patients show fluctuating disease behavior or slow, steady decline.[6] Some cycle between progression and stability, suggesting fibrosis is dynamic and may be driven by episodic triggers such as subclinical infections, microaspiration, immune flares, or environmental exposures. Genetic or epigenetic factors may also affect the lungs' ability to repair fibrosis, whereas shifts in the immune or fibrotic microenvironment, including cytokine patterns, fibroblast behavior, and vascular changes, may intermittently favor progression or quiescence. This complex and potentially reversible activity highlights the need for long-term monitoring and deeper insight into the mechanisms driving SSc-ILD progression.

The subset of patients who experience very slow but continuous progression over several years, without meeting the formal criteria for PPF, remain difficult to categorize within current definitions. In this regard, emerging data demonstrate that progression is not exclusive to high-risk phenotypes (such as patients who are ATA-positive and diffuse cutaneous). Patients with anticentromere antibodies or with less common, noncanonical antibodies may also develop ILD progression, although typically at a slower and more heterogeneous rate.[82] Recognizing this distinction is critical because it argues against complacency in so-called "lower risk" groups and instead supports a tailored approach to monitoring and treatment. This perspective strengthens the rationale that patients with slow progression should not be overlooked and may warrant therapeutic strategies comparable to those routinely considered in higher risk groups.

Finally, the optimal strategy for managing disease progression despite initial therapy (usually MMF), ie, whether to attempt second- or third-line immunosuppressive agents (eg, rituximab and tocilizumab) or initiate antifibrotics, remains to be established and calls for further systematic research to determine which approaches best improve long-term outcomes. Future therapeutic strategies will likely involve a combination of immunomodulatory and antifibrotic approaches, tailored to individual patient risk profiles rather than reliance on a single disease framework.

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