REVIEW

Combination antifibrotic and immunosuppressive therapy in progressive fibrosing ILD

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ABSTRACT

Background: Progressive fibrosing interstitial lung disease is characterized by continuous functional decline and early mortality despite conventional immunosuppressive therapy. The dual pathophysiology involves both inflammation and fibrosis and provides rationale for combination antifibrotic and immunosuppressive therapy.
Objectives: To review and synthesize current clinical evidence on the efficacy, safety, and clinical positioning of combination antifibrotic and immunosuppressive therapy in progressive fibrosing interstitial lung disease.
Methods: We conducted a comprehensive literature review of randomized controlled trials, observational studies, and real-world cohorts published between 2015 and 2025 that evaluated combined antifibrotic (nintedanib or pirfenidone) and immunosuppressive therapy in adults with non-IPF progressive fibrosing ILD. We synthesized evidence from randomized controlled trials, observational studies, and real-world data regarding their methodologies, patient population, therapies and outcomes.
Results: Forty-one studies were identified, including 14 RCTs and 12 observational cohorts. The available evidence suggests that combination therapy demonstrates promising results across various PF-ILDs. Clinical trials and real-world data have shown improved lung function and forced vital capacity with combination therapy in PF-ILD. Evidence supports combination therapy to be well-tolerated, with manageable safety and tolerability profile consistent with individual agents rather than additive effects. Limitations of the available evidence include heterogeneity of PF-ILD populations, variable background immunosuppression, and limited long-term outcome data.

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Conclusions: Combination antifibrotic and immunosuppressive therapy shows meaningful efficacy in select PF-ILD patients. Evidence supports individualized combination approaches, particularly for progressive systemic sclerosis-ILD and connective tissue disease-ILD with nonspecific interstitial pneumonia pattern. Critical evidence gaps remain regarding optimal sequencing, patient selection, and long-term outcomes, requiring future investigation.

Key words: progressive fibrosing interstitial lung disease, combination therapy, antifibrotic agents, immunosuppression, systemic sclerosis, connective tissue disease, nintedanib, pirfenidone

Introduction

Progressive fibrosing interstitial lung disease (PF-ILD) is a clinical phenotype characterized by progressive decline in lung function, worsening respiratory symptoms, and early mortality despite conventional management (1). Patients who develop a progressive fibrosing phenotype share a common trajectory of functional decline and poor prognosis, regardless of the underlying etiology. Its various etiologies include systemic sclerosis (SSc), rheumatoid arthritis (RA), inflammatory myopathies (IIM), hypersensitivity pneumonitis, and idiopathic disease (1, 2) (Figure 1). The five-year survival rate for patients with progressive pulmonary fibrosis (PPF) is approximately 64.5%, compared to 89.5% in those with non-progressive interstitial lung disease (ILD) (3).

Connective tissue disorders

ILD is a particularly significant cause of morbidity and mortality when found in patients with connective tissue diseases (CTD), with this subset emerging as the leading cause of death in SSc, contributing to approximately 35% of SSc-related mortality (4, 5). Similarly, it complicates 10-30% of rheumatoid arthritis cases and is present in up to 40% of patients with inflammatory myopathies, particularly those with anti-synthetase antibodies (6, 7). When these patients develop progressive fibrosis, defined by declining forced vital capacity (FVC), increasing fibrotic changes on high-resolution computed tomography (HRCT), or worsening symptoms despite immunosuppressive therapy, their prognosis worsens (1). Clinicians have begun to diagnose "Advanced ILD" when patients show ongoing decline in lung function, worsening CT scans, and increasing symptoms despite treatment, rather than just those in end-stage failure (46). Due to this shift in disease categorization, clinicians are often encouraged to escalate therapy at an earlier stage to limit ongoing fibrotic and immune-mediated injury, which provides justification for combining treatments when immunosuppression alone is insufficient. HRCT scans have become essential in clinical diagnosis, as they have shown the ability to detect fibrotic progression early and help predict outcomes in SSc-ILD, oftentimes before significant changes in lung function tests are observed (47).

Dual pathophysiology

The pathogenesis of PF-ILD involves interplay between both inflammatory and fibrotic pathways. While initial events may differ across disease subtypes, the progression to end-stage pulmonary fibrosis typically follows convergent mechanistic pathways (1, 3, 7). For instance, in connective tissue disease-associated ILD (CTD-ILD), autoimmune inflammation drives initial lung injury through cytokine dysregulation, immune cell infiltration, and endothelial damage. However, as disease progresses, fibrotic processes become increasingly dominant, and typically characterized by myofibroblast activation, excessive collagen deposition, and irreversible architectural distortion (1, 7). This dual pathophysiology consisting of persistent inflammation coupled with progressive fibrosis presents an opportunity for therapeutic intervention. Immunosuppressive agents such as mycophenolate mofetil,

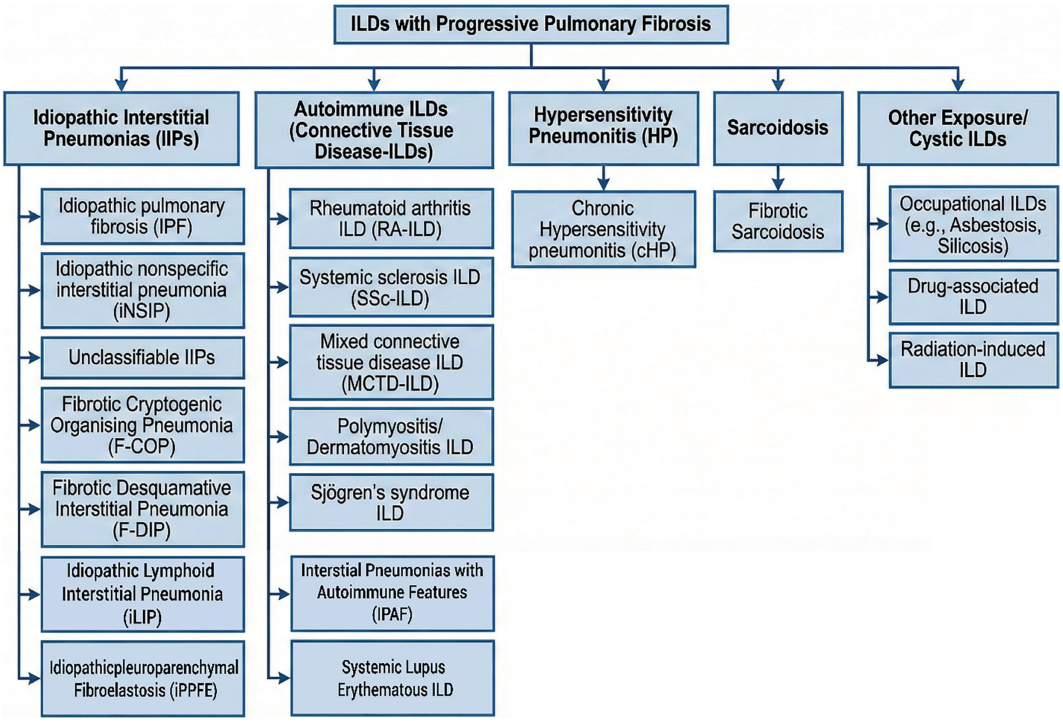

Figure 1. Interstitial lung diseases (ILDs) with progressive pulmonary fibrosis (PPF).

cyclophosphamide, and rituximab have been effective in slowing progression of CTD-ILD by targeting inflammatory pathways (6, 8, 9). However, these agents alone may be insufficient once fibrosis has established in the lungs and the fibrotic cascade has begun. Conversely, antifibrotic medications including nintedanib and pirfenidone do not affect inflammation but have shown efficacy in reducing the rate of fibrotic progression. Initially approved for IPF, these medications have shown benefit in reducing FVC decline across various fibrosing ILDs. However, they remain limited in adequately addressing the underlying inflammatory processes that immunosuppressive agents do (1, 10). The understanding that both inflammation and fibrosis drive disease progression in PF-ILD has generated considerable interest and provides a mechanistic rationale for research into combination therapeutic strategies that simultaneously target both of the pathogenic mechanisms. Immunosuppression attenuates ongoing inflammatory injury while antifibrotic therapy inhibits the fibroproliferative cascade, potentially yielding synergistic benefit when combined (11, 12). This article provides an in-depth review of most up-to-date data on the role of combination therapy in PF-ILD. We highlight its comparative efficacy and safety along with highlighting the gaps in current evidence to inform clinicians and researchers and inspire further innovations in this field.

Methods

A comprehensive literature search was conducted on PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov, from January 2015 until December 2025. The start date of January 2015 was selected based on the approval of nintedanib and pirfenidone for IPF on 15 October 2014, which marked a beginning point for investigations into antifibrotic therapy for non-IPF fibrosing lung diseases (1, 10). Keywords used for search included a combination of terms related to PF-ILD (systemic sclerosis, connective tissue disease, rheumatoid arthritis, inflammatory myopathy), antifibrotic agents

(nintedanib, pirfenidone), and immunosuppressive therapies (mycophenolate mofetil, cyclophosphamide, rituximab, azathioprine, methotrexate, tacrolimus, tocilizumab, glucocorticoids, disease-modifying antirheumatic drugs). Search terms were combined using Boolean operators to identify studies examining combination antifibrotic and immunosuppressive therapy. Relevant articles were screened by titles and abstracts, followed by full text screening of the eligible studies. Reference lists of included studies and relevant systematic reviews were manually searched to identify additional studies. After removal of duplicates, only English language articles of any study design were considered.

Studies were considered eligible if they (A) included adult patients (≥18 years) with non-IPF PF-ILD of any etiology, (B) used antifibrotic agent in combination with any immunosuppressive or immunomodulatory therapy, (C) reported at least one of the following outcomes: change in forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLCO), mortality, progression-free survival, time to disease progression, adverse events and safety outcomes, treatment discontinuation rates, and quality of life measures. Excluded were animal and in vitro studies, narrative reviews, conference abstracts or editorials without original analysis, and studies not directly addressing PF-ILD. This review adhered to the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines.

Study quality was assessed qualitatively based on study design and sample size with greater weight given to randomized controlled trials. Forty-one studies were identified, including 14 RCTs and 12 observational cohorts.

Results

Immunosuppressive therapy

Immunosuppressive therapy has been the primary treatment for CTD-associated ILD. The Scleroderma Lung Study (SLS) I trial published in 2006, established cyclophosphamide as an effective treatment for SSc-ILD, showing modest but significant improvement in FVC compared to placebo (13). Subsequently, the SLS II trial in 2016 showed that mycophenolate mofetil was non-inferior to cyclophosphamide with a more favorable safety profile, leading to widespread adoption of mycophenolate as first-line therapy for SSc-ILD (9). The focuSSced trial suggested tocilizumab (an immunosuppressant) would preserve lung function in early SSc-ILD and elevated acute-phase reactants (14). More recently, rituximab has also emerged as an effective option, with the RECITAL trial demonstrating equivalence to cyclophosphamide and the EVER-ILD trial revealing the superiority of rituximab combined with mycophenolate over mycophenolate alone in patients with ILD characterized by a non-specific interstitial pneumonia (NSIP) pattern (6, 8). Despite these positive factors, immunosuppressive monotherapy has limitations. Many patients continue to progress despite aggressive immunosuppression; particularly those with established fibrosis or a usual interstitial pneumonia (UIP) pattern on HRCT (6, 7). Also, the delayed onset of immunosuppressive agents, often requiring 6-12 months before a patient experiences benefit, leaves these patients vulnerable to functional decline during the initial treatment period (9).

Antifibrotic therapy

The approval of nintedanib and pirfenidone in 2014 provided clinicians with new tools to treat fibrosing lung diseases. Nintedanib, an intracellular tyrosine kinase inhibitor targeted multiple profibrotic pathways. These pathways include platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) receptors. These medications demonstrated up to 50% reduction in the annual rate of FVC decline and slowed disease progression in IPF and non-IPF ILDs (1, 15). The SENSCIS trial (2019) showed that nintedanib reduced the annual rate of FVC decline in patients with SSc-ILD by approximately 44% compared to placebo (10). Nearly half of the studies enrolled patients were receiving background mycophenolate therapy, which provides preliminary evidence that concomitant use of antifibrotic and immunosuppressive agents was feasible and safe (10, 16). The INBUILD trial (2019) extended these findings to a broader population with study participants having progressive fibrosing ILD of various etiologies, including autoimmune diseases, hypersensitivity

pneumonitis, and idiopathic NSIP. This study further showed the consistent benefit of nintedanib across disease subtypes (1). The LOTUSS trial (2016) assessed safety and tolerability of pirfenidone, an antifibrotic with anti-inflammatory and antioxidant properties, with 63.5% of enrolled SSc-ILD patients receiving concomitant mycophenolate (18). More recently, the SLS III trial directly evaluated upfront combination therapy with pirfenidone plus mycophenolate versus mycophenolate alone, though the study was terminated early due to enrollment challenges (19).

Discussion

Comparative efficacy of combination therapy

The rationale for combined antifibrotic and immunosuppressive therapy arise from several factors:

Synergistic mechanism:

Immunosuppressive and antifibrotic agents target distinct pathogenic pathways. While immunosuppression addresses T-cell activation, B-cell dysfunction, and cytokine dysregulation, antifibrotics inhibit fibroblast proliferation, myofibroblast differentiation, and extracellular matrix deposition (11, 32). Simultaneous targeting of both inflammatory and fibrotic mechanisms may provide more comprehensive disease control than either approach alone.

Temporal optimization:

Many immunosuppressive agents require several months to achieve maximal therapeutic effect. During this period, progressive fibrosis can proceed unopposed (9). Concurrent antifibrotic therapy could provide immediate inhibition of fibrotic progression while awaiting immunosuppressive efficacy, potentially preserving lung function that would otherwise be irreversibly lost.

Disease heterogeneity:

Patients with PF-ILD likely have varying contributions of inflammatory versus fibrotic processes driving their disease (2). Combination therapy may benefit a broader patient population by addressing both mechanisms, whereas monotherapy might be effective only in those with predominantly inflammatory or predominantly fibrotic disease.

Safety

Early clinical evidence suggested that antifibrotic and immunosuppressive agents could be co-administered without prohibitive toxicity. The gastrointestinal side effects common to both drug classes raised concerns about tolerability, but preliminary data from SENSCIS, LOTUSS, and other studies indicated that combination therapy was generally manageable with appropriate dose adjustments and supportive care (16, 18). Figure 2 depicts the synergistic mechanisms of antifibrotic and immunosuppressant drugs. Combination therapy constitutes a major milestone in the management of progressive fibrosing lung diseases. Current trials are evaluating the addition of antifibrotics to established immunosuppressive therapies for PF-ILDs. A summary of the latest clinical guidelines (4, 5, 20) integrating combination therapy for ILDs is presented in Table 1.

Immunosuppressive therapy works upstream by controlling immune activation and inflammatory signals. Antifibrotic agents work downstream by blocking fibroblast growth, scar tissue formation, and collagen buildup. It is this complementary mechanism that makes them logical partners in treating progressive fibrotic ILD (Figure 2).

Clinical evidence

Scleroderma lung study III trial

The only randomized control trial designed to test upfront antifibrotic + immunosuppressive combination therapy (SLS III) found no significant difference in FVC change between combined pirfenidone-mycophenolate and mycophenolate alone. However, the trial was underpowered (34% enrollment) and was terminated early (19). Both groups improved in FVC, consistent with known mycophenolate benefits. The combination therapy was generally well tolerated, with adverse events similar to monotherapy (19). Because SLS III was underpowered, it neither demonstrates

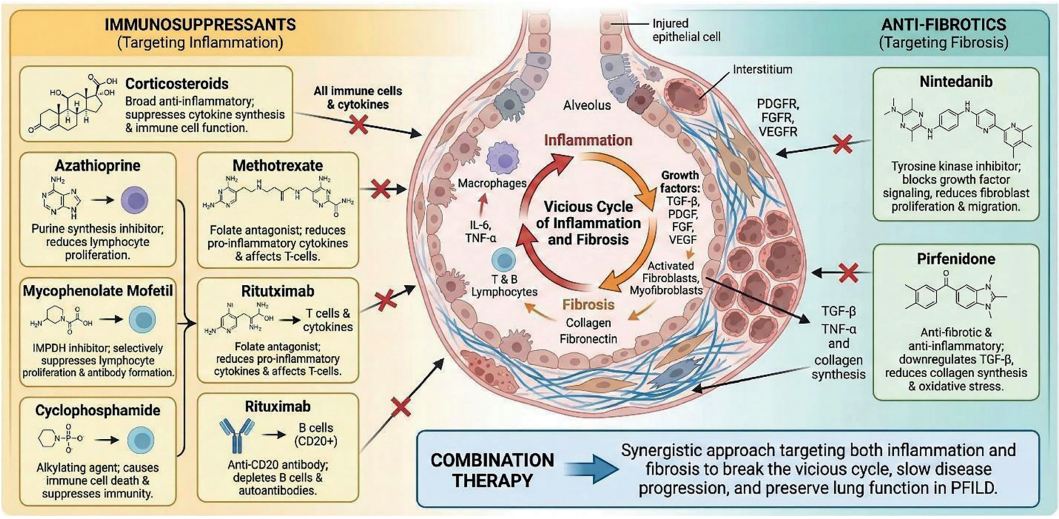

Figure 2. Mechanism of Action for Combination Antifibrotic and Immunosuppressive Therapy in PF-ILD.

nor excludes combination therapy benefit, but it does help to confirm feasibility and safety. Given its limitations, we rely on studies evaluating new therapies against background immunosuppression, typically mycophenolate.

SENSCIS trial

In the SENSCIS trial, combination therapy was evaluated with nintedanib amid background mycophenolate therapy. The SENSCIS trial showed that nintedanib significantly reduces annual FVC decline compared with placebo (10). A total of 576 patients were enrolled, which showed a greater annual decline in FVC with nintedanib than placebo. 50% of patients were on concurrent mycophenolate mofetil. In the subgroup analysis of patients on concomitant mycophenolate, the annual rate of FVC decline was lower with nintedanib plus mycophenolate (26.3 mL/year) than with nintedanib alone (55.4 mL/year). This finding suggests a synergistic advantage for combining antifibrotic and immunomodulatory agents (16). Side effects including diarrhea, nausea, and liver enzyme elevations were similar in magnitude to nintedanib monotherapy alone (16). Long-term extension data (SENSCIS-ON) also showed stability of lung function and no safety concerns (21, 22).

RECITAL trial

RECITAL (2022) tested immunosuppressants rituximab vs. cyclophosphamide. The trial showed that aggressive immunosuppression improves FVC substantially in inflammatory-predominant CTD-ILD (97–346 mL depending on subtype) but only offers stabilization in SSc-ILD (-3 to -26 mL) (6, 23). Both agents yielded only modest improvements in lung function, providing evidence of clinicians concerns regarding the limitation of targeting inflammation alone in progressive fibrotic disease. This trial indirectly suggests a potential additive effect could be achieved by combining immunosuppressants with an antifibrotic agent. The favorable tolerability profile of rituximab makes it a suitable candidate for use as the immunosuppressive component in a long-term combination regimen. RECITAL reinforced the mechanistic premise that concurrently suppressing the immunologic trigger and the downstream fibrotic response may be necessary to surpass the efficacy ceiling observed with single-pathway therapy.

INBUILD trial

In the INBUILD trial of 663 patients, 36 (10%) of 332 patients in nintedanib group were initiated on immunosuppressant therapy over 52 weeks, establishing

Table 1. The Integration of Combination Therapy (Antifibrotic plus Immunosuppressant) in Clinical Guidelines for PF-ILDs.

Guidelines / Organization	First-Line Therapy	Second-line therapy (Progression)	Third Line and Subsequent Therapies	Combination Therapy	Notes
ATS/ERS/JRS/ALAT Clinical Practice Guideline 2022 (IPF and PPF)	Standard management dependent on the specific ILD (e.g., antigen remediation for HP, immunosuppression for CTD-ILD, or observation)	Nintedanib conditionally recommended for PPF after failure of standard management (typically immunosuppression), effectively endorsing a sequential combination approach	-	Further research recommended into the efficacy and safety of Pirfenidone for non-IPF PPF	-
ATS Clinical Practice Guideline 2023 (SSc-ILD)	Mycophenolate	Add-on or switch to Cyclophosphamide, Rituximab, Tocilizumab, or Nintedanib	Nintedanib + Mycophenolate conditionally suggested as a treatment option, acknowledged increased gastrointestinal side effects	Pirfenidone and combined Pirfenidone + Mycophenolate recommended for further research due to insufficient evidence	Calls for research comparing initial combination therapy versus a sequential approach to treatment
ACR/CHEST Guideline 2023 (SARD-ILD)	Immunosuppression with Mycophenolate (preferred), Azathioprine, Rituximab, or Cyclophosphamide	Switch/Add: Tocilizumab, Rituximab, or Cyclophosphamide. Add Antifibrotic: Nintedanib for SSc-ILD, Pirfenidone for RA-ILD	IVIG, Plasma Exchange, or referral for Stem Cell/Lung Transplant	Conditionally recommends against upfront combination of Nintedanib or Pirfenidone with Mycophenolate over Mycophenolate alone. Conditionally recommends adding Nintedanib/Pirfenidone only after evidence of ILD progression.	Recommends prioritizing immunosuppression first due to cost and side effects of antifibrotics.

Abbreviations: ACR: American College of Rheumatology; ATS: American Thoracic Society; CHEST: American College of Chest Physicians; CTD-ILD: Connective Tissue Disease-associated Interstitial Lung Disease; HP: Hypersensitivity Pneumonitis; IVIG: Intravenous Immunoglobulin; PPF: Progressive Pulmonary Fibrosis; RA-ILD: Rheumatoid Arthritis-associated Interstitial Lung Disease; SARD-ILD: Systemic Autoimmune Rheumatic Disease-associated Interstitial Lung Disease; SSc-ILD: Systemic Sclerosis-associated Interstitial Lung Disease; IPF: Idiopathic Pulmonary Fibrosis.

antifibrotic efficacy across diverse PF-ILD populations (1). In autoimmune ILD subgroups, nintedanib reduced FVC decline regardless of baseline disease-modifying anti-rheumatic drug or glucocorticoid use, supporting additive benefit when combined with immunosuppressive therapy (7). Post-hoc analyses confirmed consistent efficacy even when patients initiated additional immunosuppression during the trial (24). Subgroup analyses in the Japanese population exhibited consistent results (25). Safety analyses showed no increase in serious adverse events attributable to immunosuppressive background therapy (26, 27).

RELIEF trial

The RELIEF trial analyzed patients with unclassifiable ILD and SSc-ILD where combined pirfenidone and mycophenolate mofetil therapy resulted in benefit (28). In the trial, patients with pirfenidone experienced fewer respiratory infections compared to the placebo group. This may be explained by inhibition of TGF-β by pirfenidone in a predominantly immunosuppressant-treated cohort (70% of patients). Both immunosuppressant therapy and active TGF-β signaling are known to elevate infection risk. The antifibrotic agent pirfenidone, a TGF-β inhibitor, may mitigate this risk in immunosuppressed patients by counteracting the pro-infectious pathway. This is supported by contrasting clinical data: the ASCEND trial in IPF patients not on immunosuppression showed pirfenidone did not reduce infection rates, as their baseline immunocompetence rendered this mechanism less relevant (29). Conversely, patients in the RELIEF trial were on background immunosuppression and thus at higher baseline risk, demonstrated a lower incidence of infections when treated with pirfenidone.

TOP-ILD trial

The multi-center TOP-ILD trial (2025) demonstrated that upfront combination therapy with the antifibrotic nintedanib and anti-inflammatory agents (tacrolimus and prednisolone) reversed lung function decline, improving the relative % FVC decline slope from −20.9%/year before treatment to +11.2%/year after 24 weeks of treatment (30). This translated to a 32.1%/year absolute improvement in the decline slope. Clinically, patients experienced a mean absolute increase in % FVC of 3.8% from baseline. Subgroup analysis suggested greater benefit in patients with evidence of active inflammation, such as bronchoalveolar lavage lymphocytosis or elevated blood biomarkers (e.g., C-reactive protein, Krebs von den Lungen-6). The safety profile was manageable, with diarrhea and hepatic enzyme elevations being the most common adverse events; no severe adverse events or treatment discontinuations were reported.

EVER-ILD trial

The EVER-ILD trial (2023) showed that rituximab + mycophenolate significantly improved FVC and reduced progression risk compared with mycophenolate alone in NSIP-pattern ILD (31). Benefits were consistent across CTD-ILD, interstitial pneumonia with autoimmune features (IPAF), and idiopathic NSIP. One-year follow-up showed attenuation of the FVC difference after rituximab discontinuation but continued improvement in progression-free survival (31). Safety was acceptable, with slightly higher but manageable infection rates (8). The EVER-ILD study most clearly supports early intensification of immunosuppression in inflammatory phenotypes (NSIP pattern). Patients already received months of immunosuppression yet still benefited from rituximab addition, indicating persistent inflammatory activity rather than predominantly fibrotic disease. This complements the SENSCIS and INBUILD pattern: immunosuppression helps most when inflammation predominates, and antifibrotics help even when immunosuppression is insufficient. The findings support a treatment model where inflammatory and fibrotic pathways often operate in parallel, with each patient's phenotype existing along this continuum. Combination therapy is most useful for patients with mixed inflammatory-fibrotic disease, while pure inflammatory disease may respond to immunosuppression alone and advanced fibrosis may benefit primarily from antifibrotics. A summary of recent clinical trials with direct or indirect use of combination anti-fibrotic and immunosuppressant therapy is demonstrated in Table 2.

Table 2. Recent Clinical Trials exploring Combination Therapy in PF-ILDs.

Study	Phase	Study Population	Intervention	Primary Outcome(s)	Estimated Enrolled
INBUILD: Nintedanib in PF-ILDs (NCT02999178)	Phase 3, randomized, double-blind, placebo-controlled trial	18+ years with fibrosing lung disease on HRCT	Nintedanib versus placebo; Immunosuppressive therapy in 10% nintedanib patients started over 52 weeks	Annual rate of change in FVC	663 patients
RELIEF: Pirfenidone in PF-ILDs (DRKS00009822)	Phase 2b randomized, double-blind, placebo-controlled trial	18–80 years with non-IPF PF-ILD	Pirfenidone versus placebo; 73% pirfenidone patients under immunosuppressants	Absolute change in predicted FVC %	127 patients
SENSCIS: Nintedanib for SSc-ILD (NCT02597933)	Phase 3 randomized, double-blind, placebo-controlled trial	SSc with an onset of the first non-Raynaud's symptom within the past 7 years and a HRCT that showed fibrosis affecting at least 10% of the lungs	Nintedanib vs placebo; 50% patients on mycophenolate mofetil therapy	Annual rate of decline in FVC	576 patients
RECITAL: Rituximab Versus Cyclophosphamide for CTD-ILD (NCT01862926)	Phase 2b trial randomized, double-blind, double-dummy trial	18–80 years with severe or progressive ILD related to scleroderma, idiopathic inflammatory myositis, or mixed CTD	Rituximab vs Cyclophosphamide	Rate of change in FVC	101 patients
SLS-III: Pirfenidone With MMF for SSc-ILD (NCT03221257)	Phase 2 multicenter randomized double-blind, placebo-controlled trial	18+ years diagnosed SSc with FVC ≤85% at screening, dyspnea grade 2, GGO, onset of the first non-Raynaud manifestation of SSc within the prior 84 months	MMF + Pirfenidone vs MMF + Placebo	Change in predicted FVC %	51 patients
TOP-ILD: Nintedanib and anti-inflammatory agents for PPF (jRCTs071230004)	Phase 2 multicenter, single-arm trial	20 years or older with diagnosis of Unclassifiable IIP, iNSIP, fibrotic HP, RA-ILD (all with evidence of PPF)	Tacrolimus (0.0375 mg/kg twice daily) and prednisolone (10 mg once daily) were initiated on day 1, with nintedanib (150 mg twice daily) added on day 8	Change in relative decline slope for FVC %	34 patients
EVER-ILD: Rituximab and MMF for ILD (NCT02990286)	Phase 3 randomized, double-blind, two-parallel group, placebo-controlled trial	18+ years with a diagnosis of CTD-ILD or IIP	Rituximab + MMF vs MMF alone	Change in predicted FVC %	122 patients

Abbreviations: ILD: Interstitial Lung Disease; PPF: Progressive Pulmonary Fibrosis; IPF: Idiopathic Pulmonary Fibrosis; HRCT: high-resolution computed tomographic scan; SSc-ILD: Systemic Sclerosis–Associated ILD; CTD-ILD: Connective Tissue Disease-ILD; GGO: Ground Glass Opacification; MMF: Mycophenolate mofetil; IIP: Idiopathic Interstitial Pneumonia; IIP: Idiopathic Interstitial Pneumonia; iNSIP: Idiopathic non-specific interstitial pneumonia; HP: Hypersensitivity Pneumonitis; RA-ILD: Rheumatoid Arthritis-associated Interstitial Lung Disease.

Evidence from real world data

Real-world studies indicate that both nintedanib and pirfenidone are effective and tolerable when used in combination with immunosuppressive therapy for PF-ILD. In a prospective Turkish cohort, nintedanib combined with immunosuppressants led to a significant improvement in mean % predicted FVC from 82.8 ± 17.6 % to 92.3 ± 15.8 % over 6 months, with over 60% of patients showing stable or improved HRCT findings (32). Adverse events were manageable, and no treatment discontinuations occurred. Combination therapy also improved FVC for myositis-associated ILD (33). A Real-world UK national service evaluation of 1,120 PF-ILD patients confirmed that nintedanib is widely used with concomitant immunosuppression (e.g., corticosteroids in 54.4% and mycophenolate in 31.7% of patients), finding acceptable real-world tolerability with an 18.8% overall discontinuation rate (34). Also, a 24-week prospective controlled Chinese study found that adding pirfenidone to background immunosuppression significantly improved pulmonary function in CTD-ILD subsets, including patients with SSc, IIM, and RA, with the greatest benefits seen among those with a UIP pattern in SSc and a non-UIP pattern in IIM and RA (35). Similarly, a Finnish case series of seven patients documents low dose combination therapy of cyclophosphamide with pirfenidone for refractory CTD-ILD which was well-tolerated (36). Successful treatment of rapidly progressive-interstitial lung disease (RP-ILD) with combination intensive immunosuppression plus nintedanib is also reported (37). In a retrospective study by Zhu et al. 2021, rituximab + mycophenolate did not show superior efficacy over mycophenolate alone in improving lung function in CTD-ILD population with longer disease duration. However, the rituximab cohort was associated with a greater reduction in daily prednisone use, which may be beneficial for minimizing steroid-related side effects. These findings run contrary to the EVER-LID trial which displayed higher efficacy of rituximab. This could be attributed to retrospective design of study, small sample size, and baseline imbalances between groups (38). A real-world observational analysis using Japanese health insurance claims data of 24,812 patients across IPF, PPF (auto-immune and non-autoimmune), and SSc-ILD showed that antifibrotics were predominantly used as first-line treatment in IPF, while for SSc-ILD and PPF, nintedanib was more commonly initiated after or concurrently with glucocorticoid/immunosuppressant therapy (39).

Comparison with current clinical guidelines

The 2022 ATS/ERS/JRS/ALAT PPF Guideline emphasizes the "progressive phenotype" approach, supported by the INBUILD trial (1, 4). The approach emphasizes diagnosing and managing ILD according to evidence of ongoing progression, such as declining lung function, rather than by underlying etiology. Under this model, any ILD demonstrating persistent progression is managed as PF-ILD regardless of its original disease classification. The American Thoracic Society also issued a separate conditional recommendation (2023 ATS SSc-ILD Guideline) for nintedanib plus mycophenolate, driven mainly by SENSCIS subgroup data (5). However, only 7% of the panel supported a strong recommendation. ATS also called for research comparing upfront versus sequential therapy, one of the main gaps highlighted by this review (5). Both of these guidelines predate the EVER-ILD trial, whose findings strengthen the rationale for targeted combination therapy in inflammatory phenotypes (8). The American College of Rheumatology and American College of Chest Physicians released a guideline in 2024 (2024 ACR/CHEST CTD-ILD Guideline) that conditionally recommended against upfront antifibrotic + mycophenolate combinations, largely because of limited data and concerns about cost and tolerability (20). Timely diagnosis and initiation of therapies is crucial for improving health-related outcomes in PF-ILD. Immunosuppressants remain the primary agents in non-IPF ILDs while early initiation of anti-fibrotic therapy is necessary when progressive phenotype is detected. This is because immunosuppressants don't benefit once the fibrotic pathway is set in. Based on the evidence summarized from clinical guidelines and trials, Figure 3 represents a management plan demonstrating the settings in which combination therapy should be administered.

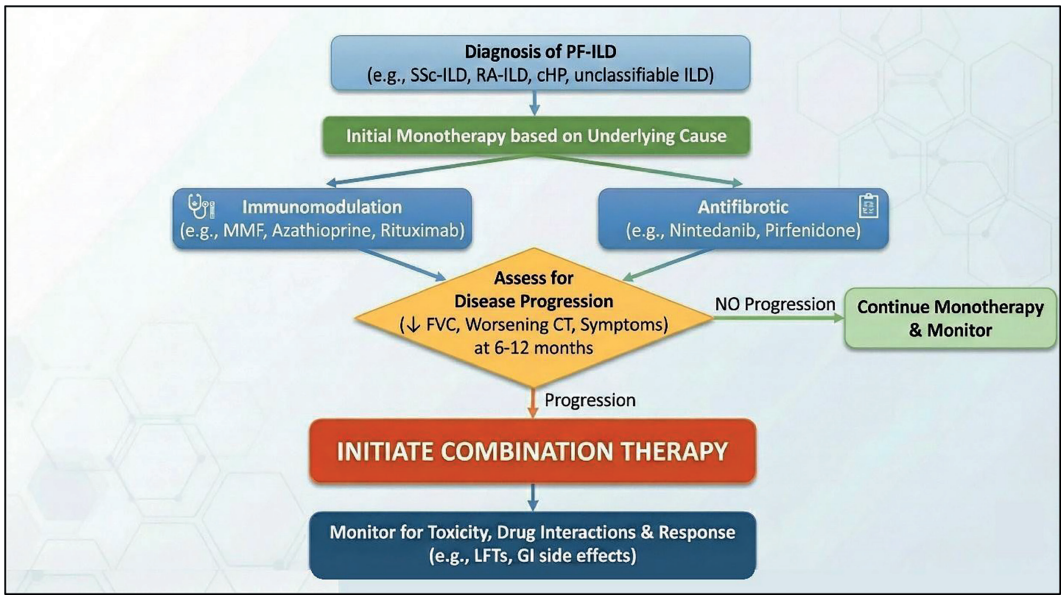

Figure 3. Clinical Management Algorithm for Initiating Combination Therapy in PF-ILD.

Tolerability

Across studies, gastrointestinal toxicity was the most frequent adverse effect, primarily driven by nintedanib or pirfenidone, but typically manageable with dose adjustments and supportive therapy (10, 16, 18, 19). Serious adverse events including infections with rituximab-based regimens were not substantially higher with combination therapy than with monotherapy (8, 26). Hepatotoxicity was uncommon and manageable (2). Overall, tolerability was acceptable, and treatment discontinuation rates (15–25%) were consistent with expectations for advanced ILD treatments (16, 19, 26). Combination anti-fibrotic therapies such as nintedanib and pirfenidone have shown manageable safety profiles (40, 41). Adverse events incidence is lower with pirfenidone than with nintedanib, but both are below the rates observed in clinical trials with no major safety concerns. Discontinuation rates due to adverse events are consistent with trial data, supporting their tolerability (42). Real-world mortality and adverse event-related IPF progression rates are higher than in clinical trials, especially for pirfenidone. Further large-scale studies are needed to clarify these risks. Concerns about additive toxicity have not been supported by the evidence (Table 3). Gastrointestinal events, particularly diarrhea are common with antifibrotics and remain so in combination regimens, but rates mirror monotherapy and are manageable (16, 26). Serious adverse events are not substantially increased, and discontinuation rates of 15–25% are acceptable given disease severity (16, 19, 26). Notably, infection rates don't rise when antifibrotics are added to immunosuppression, consistent with their non-immunosuppressive mechanism (8, 16, 26). Data from the FDA adverse event reporting system database shows a total of 35,804 and 20,486 adverse event reports in US Food and Drug Administration Adverse Event Reporting System for pirfenidone and nintedanib, respectively (43). Pirfenidone is more associated with skin reactions and photosensitivity, advising sun protection while nintedanib carries higher risks of early gastrointestinal issues, liver injury, and bleeding events, warranting close monitoring of liver function and bleeding signs.

Cost feasibility

The cost of medication represents a substantial barrier to combination therapy: antifibrotics can cost up to $120,000 per year and access often depends on insurance coverage, manufacturer assistance programs,

Table 3. Summary of adverse event profiles reported across key randomized trials and cohort studies evaluating antifibrotic, immunosuppressive, and combination therapies in progressive fibrosing interstitial lung disease.

Study	Therapy	Most common adverse events	Serious / severe adverse events	Discontinuation or management notes
INBUILD	Nintedanib vs placebo	Diarrhea (66.9%), nausea, vomiting, abdominal pain, weight loss; liver enzyme elevations	Serious AEs similar to placebo; fatal AEs lower with nintedanib (3.3% vs 5.1%)	Dose reduction (33.1%) and discontinuation (19.6%) mainly due to diarrhea; liver enzyme elevations reversible with dose adjustment
INBUILD subgroup analysis	Nintedanib vs placebo (by ILD subtype)	Diarrhea, nausea, vomiting, weight decrease, liver enzyme increases across all subgroups	Serious and fatal AEs consistent with overall population	Safety profile consistent across ILD subtypes
SENSCIS	Nintedanib vs placebo	Diarrhea (75.7%), nausea, vomiting, abdominal pain, weight loss	Serious AEs: 24.0% vs 21.5%; fatal AEs rare	Discontinuation more frequent with nintedanib (16.0% vs 8.7%)
SLS III	MMF + pirfenidone vs MMF + placebo	GI distress (55.6%), photosensitivity (11.1%), infections	9 serious AEs; no deaths	Higher GI toxicity in combination arm; most discontinuations occurred early
RECITAL	Rituximab vs cyclophosphamide	GI, respiratory, nervous system disorders (higher with cyclophosphamide)	Serious AEs similar (29 vs 33 events)	Rituximab associated with fewer overall adverse events
EVER-ILD	Rituximab + MMF vs placebo + MMF	Infections, respiratory and cardiac disorders	Serious AEs in ~40% of both groups; deaths due to respiratory failure	Infusion reactions uncommon; no fatal AEs attributed to combination therapy
RELIEF	Pirfenidone vs placebo	Nausea, dyspnea, diarrhea (grade 3–4)	Infections most common serious AE	Fewer deaths in pirfenidone group (2% vs 8%)
TOP-ILD	Upfront combination therapy	Diarrhea (67.6%), hepatic dysfunction (29.4%)	No severe adverse events	Adverse events manageable; no treatment discontinuations
Dual antifibrotic (IPF)	Pirfenidone + nintedanib	Diarrhea, anorexia, dyspepsia/ abdominal pain	Serious AEs included acute exacerbations and infections	Discontinuation often related to GI toxicity or financial reasons

or foundation support (44, 45). Cost-effectiveness analyses are needed to guide payer policy after combination therapy becomes more widely supported by evidence (43, 44).

Challenges and limitations

No adequately powered trial has compared upfront combination antifibrotic and immunosuppressive therapy versus sequential addition. Optimal sequencing including immunosuppression first, antifibrotic first, or simultaneous initiation remains untested. Current evidence derives from trials where antifibrotic agents were added to pre-existing mycophenolate therapy. Challenges with baseline differences between intervention and control groups may confound comparisons. Furthermore, predictors of response to combination therapy versus monotherapy are undefined and long-term outcomes such as mortality and transplant-free survival beyond two years are limited. Lastly, reporting of heterogeneous outcome measures such as trials using varying FVC definitions (absolute mL, % predicted, annual rate of decline) limit quantitative synthesis. Standardization would facilitate future meta-analyses. Important evidence gaps include substantial heterogeneity in PF-ILD phenotypes, variability in background immunosuppression and radiologic patterns, and challenges in trial design and patient selection that limit generalizability and identification of optimal candidates for combination therapy.

Future research directions

First, an adequately powered randomized trial comparing upfront combination antifibrotic and immunosuppressive therapy versus sequential addition strategies is needed to definitively address optimal treatment and timing (4, 5, 20). Second, predictive biomarker studies are essential to identify which patients benefit most from combination versus monotherapy, including evaluation of radiologic patterns, autoantibody profiles, and novel molecular markers (1, 2, 8). Third, comparative effectiveness research examining different combination strategies (nintedanib versus pirfenidone; mycophenolate versus rituximab versus cyclophosphamide) would help find optimal agent selection (8, 6). Fourth, long-term outcome studies extending beyond typical trial durations are needed to determine whether slowing FVC decline translates to mortality benefit and sustained disease control (1, 8, 10). Fifth, economic evaluations incorporating cost-effectiveness analyses are essential given annual antifibrotic costs exceeding $100,000 (17, 22, 31, 38, 39).

Conclusion

PF-ILD is a clinical condition characterized by decline of lung function and early mortality despite conventional management. The dual pathophysiology of its various diseases, involving both persistent inflammatory injury and progressive fibrotic remodeling, provides rationale for therapeutic strategies that simultaneously target both mechanisms. This comprehensive review demonstrates that combination antifibrotic and immunosuppressive therapy shows promising results across diverse PF-ILDs. Evidence supports combination therapy to be well-tolerated, with a manageable safety and tolerability profile consistent with individual agents rather than additive effects. Gastrointestinal adverse events, particularly diarrhea, are common but manageable with dose adjustments and supportive care. Serious adverse events are not substantially increased compared to monotherapy, and treatment discontinuation rates of 15-25%, while higher than single-agent approaches, are acceptable given potential benefits in a fatal disease. Long-term safety data extending to 2-3 years presented no major safety concerns emerging with prolonged use. An adequately powered randomized trial comparing upfront combination antifibrotic and immunosuppressive therapy versus sequential addition strategies is needed to definitively address optimal treatment and timing.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Data availability: All data used in this review are available in the published articles cited in the reference list.

Ethics statement: Ethical approval was not required for this review as it utilized previously published data from the existing literature and did not involve primary data collection from human subjects. No identifiable patient information is presented in this study.

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