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# Treatment of Interstitial Lung Diseases: Current Approaches and Future Directions

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# Treatment of Interstitial Lung Diseases: Current Approaches and Future Directions

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**Summary**

Interstitial lung disease (ILD) represents a large and complex group of pulmonary disorders that are often progressive, and to date, incurable. Important recent advancements have enabled a better understanding, characterization and treatment of ILDs. In this review, we summarize the current approach to ILD treatment, both pharmacologic and non-pharmacologic, including recent discoveries and practice-changing clinical trials. We further outline controversies and challenges, with discussion of evolving concepts and future research directions.

**Search Strategy and Selection Criteria**

We searched the Cochrane Library (1995-2021), MEDLINE (1964-2021), and EMBASE (1974-2021). We used the search terms “pulmonary fibrosis” or “interstitial lung disease” in combination with the terms “treatment” or “trial”. We largely selected publications from the past five years but did not exclude commonly referenced, relevant or highly regarded older publications. The reference lists of articles identified by this search strategy were reviewed and those judged relevant included in this review. Clinicaltrials.gov was also searched to identify contemporaneous trials of therapeutic interventions to provide readers with a list of ongoing and relevant studies.

## Introduction

The Interstitial Lung Diseases (ILD) are a heterogeneous group of disorders characterized by inflammation and/or fibrosis of the pulmonary parenchyma. Early therapeutic options were few, given the limited understanding of disease pathobiology and treatment targets. However, recent work has identified effective therapies for many forms of ILD. These successes have influenced the evolving conceptual framework of ILD disease activity, behavior, and response to treatment. This review synthesizes the current approach to pharmacologic and non-pharmacologic management of ILD, presents recent discoveries that inform the changing treatment landscape, and explores novel therapeutics in development.

## 1. Current Approach to ILD Treatment

Early understanding of ILDs, coupled with limited treatment options, led to the clinical conceptualization of steroid-responsive vs. non-steroid responsive ILD. Most ILDs were presumed inflammatory, and thus likely to respond to corticosteroids and other immunosuppressives. Over time, idiopathic pulmonary fibrosis (IPF) was considered the prototype ILD that did not respond to corticosteroids or other immunosuppressive medications. While the field has evolved beyond this simple understanding of ILD, there remains a treatment division between immunomodulatory or antifibrotic (the colloquial term “antifibrotic” is used in this manuscript to refer to medications first shown to slow progression of IPF) drugs, with the former used in ILDs associated with connective tissue diseases (CTD-ILD), hypersensitivity pneumonitis (HP), nonspecific interstitial pneumonitis (NSIP) and other presumptive “inflammatory” diseases, and antifibrotics mainly used in IPF. While this stratification of ILDs is

somewhat arbitrary as “inflammatory” ILDs can progress to a predominantly fibrotic phenotype(1), this section summarizes the use of immunomodulatory medications for ILDs characterized predominantly by inflammation, then the antifibrotics used predominantly to treat IPF (**Figure 1**).

**Immunomodulatory Therapies**

Corticosteroids are among the first immunomodulatory drugs developed to treat inflammatory diseases. Nevertheless, there are few prospective double blind randomized controlled trials (RCT) studying their efficacy in ILDs. One example is a small randomized trial comparing outcomes of patients with acute HP randomized to placebo or prednisone(2). In this study, patients treated with prednisone had more rapid improvement in forced vital capacity (FVC) and diffusion capacity of carbon monoxide (DLCO), although both groups ultimately had similar lung function at the end of the trial. Data supporting the use of corticosteroids for other ILDs is limited to retrospective case series. Such studies have shown corticosteroid use to be associated with improvement in lung function and better survival in patients with NSIP(3), and organizing pneumonia(4). Often, they are used as first-line therapy for ILDs due to relatively quick onset of action, but their use is based more on anecdote and experience than robust evidence.

Azathioprine is a purine analogue that suppresses the immune system by inhibiting DNA synthesis. There are no published randomized trial data informing its efficacy for managing

ILDs. However, cohort data suggest that its use may improve lung function in patients with scleroderma(5), HP(6), and dermatomyositis(7, 8).

Cyclophosphamide (CYC) is a prodrug that is converted to phosphoramide mustard, which forms DNA crosslinks leading to cellular apoptosis. The efficacy of CYC for managing systemic sclerosis-ILD (SSc-ILD) was studied in a prospective placebo-controlled trial(9) where patients treated with CYC had significantly less loss of FVC compared to placebo controls after 12 months, suggesting that CYC is an effective treatment for SSc-ILD. In addition, use of CYC has been associated with favorable outcomes in ILD associated with inflammatory myopathies(7, 10). Data supporting its use for managing ILDs such as HP or rheumatoid arthritis-associated (RA-ILD) are lacking.

Mycophenolate Mofetil (MMF) is the prodrug of mycophenolic acid, which inhibits DNA synthesis and cell proliferation by blocking formation of guanine nucleotides via the de novo pathway(11). Because lymphocytes generate guanine solely via the de novo pathway, they are a relatively specific target of MMF (unlike azathioprine, which may target any dividing cell). The efficacy of MMF for managing SSc-ILD was compared to CYC, demonstrating that patients receiving 1.5 grams per day of MMF had a 2.2% improvement in FVC two years after initiating therapy, with the majority of improvement occurring within the first 12 months(12). Retrospective case studies have reported that MMF may stabilize or improve lung function in patients with HP(6, 13), and CTD-ILD(14) including inflammatory myopathies(8).

Rituximab is a humanized monoclonal antibody that binds to CD20 expressed on B-cells. When bound to CD20, rituximab enhances their clearance by apoptosis or by natural killer cells. Although randomized trials are lacking, uncontrolled studies have reported an association between the use of rituximab and improved lung function in patients with SSc-ILD(15), inflammatory myopathies(16), and HP(17). Although these reports suggest that rituximab may be useful for treating a subset of ILD patients, they need validation in larger prospective randomized trials.

The humanized monoclonal antibody tocilizumab binds to both soluble and membrane bound IL-6 receptors blocking IL-6 signaling. Two randomized, double blind placebo-controlled trials studied the efficacy of tocilizumab for treatment of early scleroderma(18, 19). Although lung function was a secondary endpoint, both studies reported that SSc-ILD patients treated with tocilizumab had slower loss of FVC compared to the control arm (-0.4% vs. -4.6%). Based on these data, tocilizumab was approved in the United States (US) for treatment of SSc-ILD. In addition to treating early SSc-ILD, case series have reported that tocilizumab may also be effective for treating refractory SSc-ILD(20) as well as sporadic reports that it may be useful for treating RA-ILD(21, 22), and anti-synthetase syndrome(23). Again, these anecdotal reports need validation in prospective randomized trials.

Additional immunosuppressive medications may have biological activity against ILDs but have limited data supporting their use. These include tofacitinib, leflunomide, abatacept, tacrolimus, among others. Of these, tacrolimus (or other calcineurin inhibitors) may improve lung function in patients with anti-synthetase syndrome-associated ILD(24), but again further data are

needed to inform its role in disease management. With the exception of randomized trials, data informing the efficacy and role of these immunomodulatory drugs are of generally low quality, limiting confidence in the conclusions.

**Antifibrotic Therapies**

Early clinical trials in patients with IPF suggested improved survival with combined immunosuppressant therapies, which remained the standard of care for several years(25). In 2012, the PANTHER trial demonstrated that patients treated with prednisolone, azathioprine and N-acetylcysteine (NAC) were at increased risk of death and hospitalization compared to untreated patients(26). In addition to PANTHER, several other clinical trials were negative, leaving an important therapeutic gap for IPF treatment. Repurposed drugs that failed to effectively treat IPF include bosentan, interferon-gamma, etanercept, imatanib, everolimus, ambrisentan and warfarin(27, 28). Standard IPF management defaulted to supportive care and clinical trial enrolment where possible.

In 2014, pirfenidone and nintedanib were reported to be equally efficacious in slowing IPF disease progression, defined as decline in FVC. In pooled analysis of the CAPACITY trials(29), patients in the pirfenidone arm had less decline in FVC% at 72 weeks, with significantly fewer patients reaching an FVC decline of 10% predicted, compared to placebo. The ASCEND study(30) showed similarly slowed FVC decline, with fewer patients experiencing a 10% FVC decline and more patients maintaining stable lung function compared to those in the placebo arm. Pooled analysis from all three phase three trials demonstrated a reduction in mortality with pirfenidone(31), including in patients with more advanced lung function impairment(32).

In two phase three trials, INPULSIS 1 and 2, nintedanib demonstrated a reduction in FVC decline compared to placebo, with evidence of prolonged time to first acute exacerbations in one of the two trials(33). In post hoc analysis, a higher proportion of patients treated with nintedanib improved or remained stable and a lower proportion had an FVC decline of >5 or >10% over 52 weeks, regardless of baseline lung function(34). Furthermore, nintedanib showed similar efficacy in patients with severe disease (DLCO < 35%)(35). Pre-specified pooled analysis demonstrated consistent effects of nintedanib across multiple patient subgroups(36). Based on these study results, pirfenidone and nintedanib have become the pharmacologic standard of care for treating IPF.

To date, trials of combination therapy have failed to demonstrate additive efficacy when combining pirfenidone or nintedanib with each other, or with drugs targeting non-fibrotic pathways, such as NAC(37), or sildenafil(38, 39). Yet, some combination therapies have sound scientific rationale in targeting multiple aspects of the fibrogenic pathway and maintain potential to provide additive impact on patient outcomes.

**Managing ILD comorbidities**

Given the high prevalence of abnormal gastro-esophageal reflux (GER) and microaspiration in patients with IPF, antacid therapy has been evaluated to treat IPF. Post-hoc analyses of placebo arms of clinical trials and retrospective studies have provided conflicting results on the risk or benefit of antacids in slowing IPF progression(40, 41). These studies are limited by confounding

and bias, and most studies did not rigorously confirm the presence of abnormal GER. With prospective trials needed to robustly address this question; a randomized trial of proton pump inhibitor therapy is currently underway in patients with IPF (Cochrane Central Register of Controlled Trials Number ISRCTN13526307). A phase two RCT of fundoplication surgery found a trend towards slowed FVC decline and numerically fewer deaths and acute exacerbations in IPF patients in the intervention arm(42). Notably this study was conducted in patients with abnormal GER documented by pH and manometry testing. While under-powered to detect the primary outcome, the study provides the most robust evidence to date supporting a possible benefit of anti-reflux surgery in a select subset of IPF patients.

Pulmonary hypertension (PH) is a frequent comorbidity in patients with ILD as a consequence of the ILD disrupting the pulmonary vasculature. In some cases, most commonly associated with CTD, pulmonary arterial hypertension is caused by primary pulmonary vascular disease coexisting with the ILD. Multiple PH-specific drugs have been tested as treatments for IPF(43-45), but none demonstrated clear evidence of benefit, beyond improved walk distance in a small subgroup in an open-label trial(45). A recent randomized trial of inhaled treprostinil was conducted in ILD patients with documented PH(46). Treprostinil therapy improved 6-minute walk distance (6MWD), reduced NT-proBNP and was associated with lower rates of clinical worsening compared with placebo. It has been recently approved by the US Food and Drug Administration (FDA) to treat PH in patients with ILD.

**Non-pharmacologic Management of ILD**

Non-pharmacologic management is central to ILD care. Symptom management, end of life planning, pulmonary rehabilitation and preventative strategies, in addition to education and support for patients and care partners are paramount. This includes patients with IPF as antifibrotics have demonstrated little impact on improving health-related quality of life (HRQL)(47). Thus, comprehensive management of ILD extends beyond pharmacologic therapy and requires a multidisciplinary and multi-dimensional approach.

Supplemental oxygen therapy should be offered to patients with severe resting hypoxemia, or isolated exertional hypoxemia in the context of symptoms or exercise-limitation(48, 49). Short-term use of ambulatory oxygen is associated with improved quality of life, endurance and exercise performance(50). An ongoing randomized trial should inform the role of long-term ambulatory oxygen in ILD patients with isolated exertional hypoxemia(51). Pulmonary rehabilitation (PR) should be considered for all patients with ILD and associated exercise limitation. PR is associated with short-term improvements in exercise endurance, symptoms and quality of life for ILD patients, although long-term benefits are less well-characterized(52). While access to PR programs may be limited by geography or resource constraints, the increasing use of virtual programming could facilitate availability if confirmed to have similar benefits as traditional PR. Routine infection prevention measures such as influenza, pneumonia, and Sars-CoV2 vaccines are imperative though not specifically studied in ILD patients. Screening for latent infections should be performed as clinically indicated for patients treated with systemic immunosuppression.

Dyspnea can be a disabling symptom that negatively affects mobility and quality of life in ILD patients. Causes of dyspnea are often multifactorial and to date, there is a paucity of data guiding its management in ILD patients. Low dose opioids are used to manage dyspnea, despite recent data suggesting they are ineffective for managing chronic dyspnea(53). Whether these findings can be extrapolated to ILD patients warrants study. Cough is another prominent symptom with disabling impact in ILD and is associated with adverse outcomes(54). Opioids are used despite a lack of robust evidence of benefit in ILD, with a randomized trial current underway (NCT04429516). Gabapentin may diminish cough frequency(55). A 24-week crossover trial of thalidomide demonstrated improvement in cough related quality of life and cough severity scores, however adverse events limit its use(56). Furthermore, a proof-of-concept study of nebulized sodium cromoglicate showed a reduction in daytime cough frequency of 31% in patients with IPF(57). Overall, evidence guiding the management of cough in ILD is limited and based on expert opinion(58) and additional prospective RCTs are needed.

Progressive lung disease with high symptom and functional burden requires multi-disciplinary support for patients and their care partners. Palliative care consultation and support may be useful early in the disease course, particularly for ILDs known to be incurable or likely to progress(59). Despite this, only a minority of patients access palliative care services even during acute care admission(60). The barriers to effective care delivery include delayed referrals regarding end-of-life decisions, fear of talking about the future, uncertainty regarding prognosis and a lack of understanding regarding the role of palliative care(61). A recent randomized trial demonstrated that a nurse-led palliative care intervention improved the preparedness and

knowledge in care partners of patients with IPF(62), highlighting the importance of multi-disciplinary care. ILD remains a leading indication for lung transplantation worldwide, representing an increasing proportion of lung transplants being performed, and appropriate patients should have early consideration and referral for transplant evaluation. While not an ILD treatment *per se*, lung transplantation remains a life-prolonging intervention and should be considered for select patients whose disease has progressed despite available pharmacotherapies(63).

**Preventative measures**

Given the abundance of agents known to cause interstitial lung injury with subsequent inflammation and scarring, primary prevention should be the ultimate goal. Although the precise etiology remains unknown in most ILD cases, various subtypes have been linked to secondary causes such as smoke inhalation, environmental exposures, occupational risk factors, medication toxicity, radiation exposure, and lung-limited or systemic infections(64). While genetic and idiopathic causes are currently not preventable, the probability of developing ILD attributable to known causes can be diminished by mitigating identifiable risk factors. Measures such as smoking cessation, avoidance of second-hand smoke, and improving air quality, especially in regions with air pollution and high particulate matter, are strongly advocated(65-67). The use of a respirator to enhance particle filtration and reduce potential lung damage from inhaled harmful substances, such as metal dust, asbestos, silica, or chemicals, especially in at-risk occupational settings, seems beneficial(68). Additional measures include avoiding pneumotoxic medications where possible. Pulmonary infections should be treated early, and

when radiation therapy or chemotherapy are considered, alternative strategies should be sought to reduce the propensity for lung injury.

Notably, more cryptic exposures may result from close contact with birds and seemingly benign hobbies such as playing wind instruments(69). In HP, a third of cases are associated with avian antigen exposure, and one in seven cases are linked to environmental molds(70). While the complexities of antigen dosing and its temporal relationship with ILD are poorly understood, environmental exposures should be avoided where feasible, especially in at-risk individuals.

## 2. Evolving Treatment Concepts

Discovery of effective therapeutics for IPF was monumental, yet the necessity of defining a study population by its clinical diagnostic label and not its biology limited drug availability and use. Clinical experience suggests that in addition to IPF, there exists a population of patients with fibrotic ILD whose disease progresses despite standard of care therapy, a phenomenon labeled progressive fibrosing ILD (PF-ILD). This phenotype of disease behaviour has been observed in a subset of patients with ILD associated with CTD, sarcoidosis, asbestosis, HP, idiopathic NSIP, and those with otherwise unclassifiable disease. Despite similar disease behaviour, approval of antifibrotics was limited to IPF. In order to resolve these limitations, clinical trials sought to test the efficacy of antifibrotics to slow disease progression in PF-ILD. It is worth emphasizing that PF-ILD is not a diagnosis but rather a descriptive phenotype of disease behaviour broadly applied to any ILD diagnosis. Whether the molecular drivers of

disease progression are shared between the various clinical diagnoses remains to be established.

Four studies have evaluated the role of antifibrotics in ILDs other than IPF; two with pirfenidone and two with nintedanib (**Table 1**). In a phase 2 study of pirfenidone in PF-ILDs, defined as an FVC decline >5% despite conventional therapy(71), the RELIEF trail showed a positive signal of slowed disease progression based on rate of FVC% decline at 48 weeks. A second phase 2 study of pirfenidone in patients with unclassifiable ILD did not meet its primary endpoint due to technical issues with daily home spirometry(72). However, secondary endpoints using conventional lab-based spirometry demonstrated that patients on pirfenidone were less likely to have an FVC decline >5% or >10% compared to placebo. The INBUILD trial assessed the safety and efficacy of nintedanib in patients with PF-ILD, defined as either >10% decline in FVC, 5-10% decline in FVC in addition to worsening symptoms or increased HRCT fibrosis, or worsening symptoms with increased HRCT fibrosis, over two years(73). Nintedanib slowed the annual rate of FVC decline by nearly 50%, a finding consistent across subgroups of usual interstitial pneumonia (UIP) and non-UIP HRCT patterns, as well as diagnostic subgroups(74). Furthermore, in a cohort of patients with SSc-ILD; the SENSCIS study, nintedanib again slowed the rate of FVC decline(75), including in patients on mycophenolate(76).

Overall, these trials inform the efficacy and role of antifibrotic therapies to treat patients with diagnoses other than IPF when the ILD is worsening despite conventional therapy. Again, while these have been sentinel, there remain many unknowns. Most urgently needed are data

guiding the use of these medications in patients who have not yet progressed but who are at high risk of progression due to baseline clinical variables or biomarkers. Also important for future work is to understand whether combination therapy should be started early in certain subgroups to target immunopathogenesis and fibrogenesis simultaneously to prevent progression via multiple pathways (**Figure 2**).

## 3. Areas of Discovery and Future Directions

### Molecular phenotyping

While there is overlap and shared response to some drugs between different diagnostic subgroups of ILD, there are limited data demonstrating that specific mechanisms of disease activity or worsening are shared across these groups. The biology of a particular disease may differ from another, may differ between patients with the same diagnosis, or even within one patient at different time-points in their disease trajectory. Furthermore, it is possible the pathobiology of a disease changes over time (e.g. transitioning from an inflammatory to a fibrotic phenotype). Full characterization of disease biology that can be used to predict response to specific targeted treatments will require biological samples that inform disease activity. Biomarker discovery is an active and dynamic area anticipated to facilitate individualized diagnostic and therapeutic approaches(77). Specific biomarkers have been identified that predict disease progression and mortality in patients with IPF. These include MMP-7, SP-D, KL-6, CA-125, CA19-9, peripheral blood leukocyte telomere length (PBL-TL), and peripheral blood monocyte count(78-80). While some of these are commercially available and

clinically actionable, they have yet to be routinely incorporated into clinical decision making. These have been largely studied in IPF, representing potential biomarkers that could be studied in non-IPF ILDs to identify individuals at risk of disease progression (ie. those with a PF-ILD phenotype). Theragnostic biomarkers predict treatment response, and ongoing work seeks to identify blood-based markers that are reliable, reproducible and ready for implementation in clinical trials and clinical care. The availability of such biomarkers will significantly impact diagnostic and management pathways and facilitate the discovery of novel effective therapeutics.

Genetic variants and markers of telomere dysfunction have important potential role as biomarkers guiding treatment and prognostication in patients with ILD. The PANTHER trial showed that combined immunosuppression in IPF patients was associated with harm, with mortality risk driven by the subgroup of patients with short telomeres (PBL-TL <10$^{th}$ percentile)(81). It is estimated that 10-12% of patients with fibrotic HP have short telomeres and or a protein altering variant in a telomere-related gene(82). Shared genetic risks have been identified across diagnostic subgroups including MUC5B promoter variants in patients with familial pulmonary fibrosis and RA-UIP, and rare protein damaging variants in telomere related genes in RA-ILD and fibrotic HP patients. These ILDs have similar disease trajectories, suggesting shared pathobiology in these groups(83, 84). Long term immunomodulatory therapy is a mainstay of treatment for many ILDs including fibrotic HP, CTD-ILD and some unclassifiable ILDs including Idiopathic Pneumonia with Autoimmune Features (IPAF). A recent retrospective study showed that while MMF may improve outcomes for some patients with fibrotic HP, this benefit

was not identified in patients with short telomeres(85). IPAF patients with short PBL-TL had more rapid loss of FVC(86). Patients with telomeropathies may represent a subgroup at risk for harm with immunosuppressive therapy and this remains a priority area for research. Further work to characterize relationships between genetics, PBL-TL and therapeutic responses will drive pharmacogenomic discoveries and enable precision medicine approaches for patients with ILD.

**Novel Therapeutics**

Several therapeutics are under investigation for the treatment of ILDs, targeting aberrant immune responses or pro-fibrotic pathways (**Tables 2 and 3**). Phase 2 RCTs assessing novel therapies in IPF frequently adopt one of the most validated outcome measures - the percent change in predicted FVC as a clinically meaningful endpoint in these studies. Many of these emerging therapeutics have demonstrated promise. A 28-week study that compared patients receiving intravenous infusions of recombinant human pentraxin 2 (PRM-151) to placebo demonstrated a 2.3% difference in FVC% in favor of PRM-151 without any increase in adverse events(87). The safety, tolerability, and efficacy of pamrevlumab, a fully human recombinant IgG kappa monoclonal antibody, was assessed in the PRAISE trial, a phase 2 RCT of subjects with IPF(88). Pamrevlumab was well tolerated and reduced the proportion of patients with disease progression (10·0% vs. 31·4%), as well as the decline in FVC% by 60·3% at week 48 (NCT01890265). Given these promising results, pamrevlumab and pentraxin 2 are in phase 3 development for IPF. Other phase 2 RCTs evaluating the efficacy, safety, and tolerability of newer IPF pharmacotherapies are currently underway. These include PLN-74809, a dual

selective inhibitor of $\alpha_v\beta_6/\alpha_v\beta_1$ that effectively blocks TGFβ activation and subsequently collagen expression (NCT04396756). DWN12088, a prolyl-tRNA synthetase inhibitor was shown to be safe and tolerable in a phase 1 IPF study, and the follow-up phase 2 RCT is in the pipeline (NCT04888715). Similarly, the oral senolytic combination of dasatinib and quercetin (DQ) was shown to alleviate IPF-related dysfunction in preclinical models. In addition, the study demonstrated a 100% retention rate with no DQ discontinuation while improving 6MWD, gait speed, and chair-stand time in an open-label Phase 1 study (NCT02874989).

Despite fewer trials than IPF, several trials are ongoing for CTD-ILDs. The TRAIL1 multicenter phase 2 RCT assesses pirfenidone's efficacy, safety, and tolerability in subjects with RA-ILD(89). Here, the primary endpoint is FVC decline of ≥10% or death over 52 weeks, and subjects may have a UIP pattern similar to IPF (NCT02808871). The RECITAL trial, a multicenter phase 2/3 RCT, compared the efficacy of rituximab against intravenous cyclophosphamide in diverse CTD-ILDs, including scleroderma, idiopathic inflammatory myositis, and mixed CTD. This recently terminated study had its primary endpoint as the absolute change in FVC over 48 weeks, and its results are awaited (NCT01862926). Another ongoing phase 2 trial, SLS-III, is focused on patients with active and symptomatic SSc-ILD. In SLS-III, the additional benefit of pirfenidone on a background therapy of MMF will be assessed by measuring the change in FVC% from baseline to 18 months (NCT03221257).

**Summary**

Treatment of ILD is complex, with a targeted approach requiring consideration of disease biology and anticipated response to specific therapies. Non-pharmacologic management and patient support is essential for comprehensive care. Key clinical trials have identified effective therapies for IPF and progressive fibrosing ILDs, as well as for specific forms of CTD-ILD. Ongoing biomarker discovery, paired with novel or combined therapeutic targets, will revolutionize the treatment landscape for patients living with ILD.

**Figure Legend**

**Figure 1: Pictorial depiction of "inflammatory" and "Fibrotic" ILDs and therapeutic targets**. This figure depicts key cellular elements of "inflammatory" ILDs in the left panel and "Fibrotic" ILDs in the right panel. Immunomodulatory and fibro-modulatory drugs targeting these key cellular elements are listed in adjacent panels. Drugs described in black text are currently used to manage patients. Drugs in red text are under investigation. * indicates drugs that may target more than one cell. AEC1= alveolar type 1 cell, AEC2= alveolar type 2 cell, DEC= dysfunctional alveolar epithelial cell.

**Figure 2: Conceptual framework for the treatment of interstitial lung disease (ILD)**. Patients with idiopathic pulmonary fibrosis (IPF) should be treated with antifibrotics (red bar). Patients with connective-tissue disease related ILD (CTD-ILD), hypersensitivity pneumonitis (HP) and unclassifiable ILD may demonstrate clinical stability, warranting monitoring (white bar), may benefit from immunomodulatory therapy (blue bar), or in scenarios with progressive fibrosis, would be expected to benefit from antifibrotic therapy. In some circumstances, patients may warrant therapy with combined immunosuppression and antifibrotics; further data are needed to inform this approach.

**Table 1. Randomized clinical trials of antifibrotic therapy for non-IPF interstitial lung diseases.**

| Trial, year | Population | Design | Primary outcome | Primary effect measure | Comments |
|---|---|---|---|---|---|
| Distler et al. *NEJM*, *2019* | 576 patients with systemic sclerosis associated ILD | Nintedanib 150mg twice daily vs. placebo x 52 weeks | Annual rate of decline in FVC at 52 weeks | Nintedanib -52.4mL/year vs. placebo -93.3mL/year Difference of 41mL/year (95%CI 2.9 to 79.0) | Findings consistent when stratified by baseline MMF use |
| Flaherty et al. *NEJM*, *2019* | 663 patients with non-IPF progressive fibrosing ILD | Nintedanib 150mg twice daily vs. placebo x 52 weeks | Annual rate of decline in FVC at 52 weeks | Nintedanib -80.8ml/year vs. placebo -187.8mL/ year Difference of 107mL/year (95%CI 65.4 to 148.5) | Findings consistent when stratified by HRCT pattern (UIP vs non-UIP) |
| Maher et al. *Lancet Resp Med*, *2020* | 253 patients with progressive fibrosing unclassifiable ILD | Pirfenidone 801mg three times daily versus placebo X 48 weeks | Mean change in FVC% predicted at 24 weeks, measured by daily home spirometry | Median change pirfenidone -87.7mL vs. placebo -157.1mL | Secondary outcome (lab-based spirometry) treatment difference 95.3mL pirfenidone vs. placebo (95%CI 35.9 to 154.6) |
| Behr et al. *Lancet Resp Med*, *2021* | 127 patients with non-IPF progressive fibrosing ILD | Pirfenidone 801mg three times daily versus placebo X 48 weeks | Absolute change in FVC% predicted at 48 weeks | Mean difference pirfenidone vs placebo 1.69% (95%CI -0.65 to 4.03) | Trial terminated prematurely. Multiple statistical approaches presented. |

Abbreviations: IPF=idiopathic pulmonary fibrosis, ILD=interstitial lung disease, UIP-usual interstitial pneumonia, FVC=forced vital capacity, mL=milliliter, MMF=mycophenolate mofetil.

**Table 2.** Select recent and emerging experimental disease modifying pharmacotherapies in idiopathic pulmonary fibrosis (IPF).

| Therapy | Mechanism of action | Primary Outcome | Status | Clinical Trial identifier |
|---|---|---|---|---|
| **IPF *(Phase I)*** | | | | |
| Autologous lung stem cells* | Immunomodulatory, and anti-proliferative | Number of patients with AEs and serious AEs; FVC change from baseline to week 48 | Recruiting | NCT04262167 NCT02745184 |
| DWN12088** | Prolyl-tRNA synthetase inhibitor | Pharmacokinetics and drug-drug interactions with currently approved antifibrotics | Recruiting | NCT03711162 NCT04888715 |
| TD-1058*** | Mechanism undefined | Number and severity of treatment emergent AEs | Recruiting | NCT04589260 |
| TRK-250*** | TGF-β1 suppression | Incidence and severity of AEs up to 7 days after last dose | Recruiting | NCT03727802 |
| **IPF *(Phase II)*** | | | | |
| BMS-986278** | LPA antagonist | Rate of change in percent predicted FVC (baseline to week 26) | Recruiting | NCT04308681 |
| C21** | Angiotensin receptor agonist | Nature and frequency of AEs occurring over the trail period | Recruiting | NCT04533022 |
| CC-90001** | Selective JNK inhibitor | Change in percentage predicted FVC from baseline to week 24 | Recruiting | NCT03142191 |
| GKT137831 (Setanaxib) ** | NOX1 and NOX4 inhibitor | Surrogate biomarker of oxidative stress by mass spectrometry from baseline to week 24 | Recruiting | NCT03865927 |
| GLPG1205** | GPR84 antagonist | Change in FVC from baseline to week 26 | Completed | NCT03725852 |
| Jaktinib DM** | JAK -1, 2, and 3 Inhibitor | Change in FVC from baseline to week 24 | Recruiting | NCT04312594 |
| KD025 (SLx-2119) ** | ROCK2 inhibitor | Change in FVC from baseline to week 24; number of subjects experiencing AEs | Active, not recruiting | NCT02688647 |
| MN-001 (tipelukast) ** | Leukotriene receptor antagonist, PDE-3, 4 inhibitor | Mean change in FVC from baseline to Week 26 | Recruiting | NCT02503657 |
| ND-L02-s0201 (BMS-986263) ** | HSP47 inhibitor | Number with treatment-related AEs (baseline to week 24) | Recruiting | NCT03538301 |
| PLN-74809** | Dual selective αVβ1/αVβ6 inhibitor | Number of study participants with treatment-related AEs and laboratory abnormalities | Recruiting | NCT04396756 |
| Saracatinib** | Highly selective Src tyrosine kinase family inhibitor | Safety, tolerability, pharmacodynamics, pharmacokinetics, efficacy (as measured by change in FVC, baseline to week 24) | Recruiting | NCT04598919 |
| TD139*** | Galectin-3 inhibitor | Rate of FVC decline (mL) from baseline to week 52 | Recruiting | NCT03832946 |
| VAY736 (ianalumab) **** | IgG1 monoclonal antibody against BAFF receptor | Change from baseline to week 48 in FVC | Recruiting | NCT03287414 |
| **IPF *(Phase III)*** | | | | |
| GLPG1690 (ziritaxestat)** | Autotaxin inhibitor | Rate of decline in FVC (baseline to week 52) | Completed | NCT03733444 NCT03711162 |
| Morphine Sulfate** | Opiate receptor agonist | Percent change in daytime cough frequency (coughs per hour) from baseline to Day 14 | Recruiting | NCT04429516 |
| Pamrevlumab (FG-3019)* | Fully human monoclonal antibody against CTGF | Change in FVC from baseline to week 52, proportion with disease progression (death, or ≥10% decline in absolute FVC percentage predicted; baseline to week 52) | Recruiting | NCT03955146 NCT04419558 |
| rhPTX-2/PRM-151* | TGF-β1 modulator | Absolute change in FVC (mL) from baseline to week 52; Incidence and severity of AEs; | Completed | NCT04552899 NCT04594707 |

**Intravenous therapy; **Oral therapy; ***Inhaled; ****Subcutaneous; Jaktinib DM= Jaktinib Dihydrochloride Monohydrate; CHP=chronic hypersensitivity pneumonitis.*

**Table 3.** Select recent and emerging experimental disease modifying pharmacotherapies in other interstitial lung diseases.

| Therapy | Mechanism of action | Primary Outcome | Status | Clinical Trial identifier |
|---|---|---|---|---|
| **CHP *(Phase III)*** | | | | |
| Pirfenidone in CHP** | May inhibit fibroblast proliferation | Change in FVC from baseline to week 52 | Completed | NCT02958917 |
| **RA-ILD *(Phase II)*** | | | | |
| Abatacept | Inhibits T-cell activation | Change in FVC from baseline to week 24 | Recruiting | NCT03084419 |
| Pirfenidone** | May inhibit fibroblast proliferation | FVC decline of ≥10% or death over 52 weeks | Recruiting | NCT02808871 |
| **RA-ILD *(Phase IV)*** | | | | |
| Tofacitinib vs. Methotrexate | Inhibits janus kinase | Change in total score of HRCT pulmonary abnormalities at 24 weeks | Recruiting | NCT04311567 |
| **ASS-ILD *(Phase III)*** | | | | |
| Cyclophosphamide and Azathioprine | Destroys proliferating B- and T- lymphoid cells. | Time from treatment initiation to first ASS-ILD related event | Recruiting | NCT03770663 |
| **SSc-ILD *(Phase II)*** | | | | |
| Pirfenidone** | May inhibit fibroblast proliferation | Change in FVC from baseline to 18 months | Active, not recruiting | NCT03221257 |
| Ixazomib | Proteasome inhibitor | Number of participants with ≥1 treatment-emergent adverse event at 7 months. | Recruiting | NCT04837131 |
| **SSc-ILD *(Phase III)*** | | | | |
| Rituximab vs. cyclophosphamide*^ | B-cell depleting agent | Absolute change in FVC over 48 weeks | Terminated | NCT01862926 |

**Intravenous therapy; **Oral therapy; ***Inhaled; ****Subcutaneous; Jaktinib DM= Jaktinib Dihydrochloride Monohydrate; CHP=chronic hypersensitivity pneumonitis. SSc-ILD = systemic sclerosis-associated interstitial lung disease. RA-ILD = rheumatoid arthritis-associated interstitial lung disease. ASS-ILD = Antisynthetase Syndrome-related Interstitial Lung Disease. ^Idiopathic inflammatory myositis, and mixed connective tissue disease also assessed. +IIP=Idiopathic interstitial pneumonia. CHP, occupational ILD, combined pulmonary fibrosis and emphysema, and CTDILD also assessed.*

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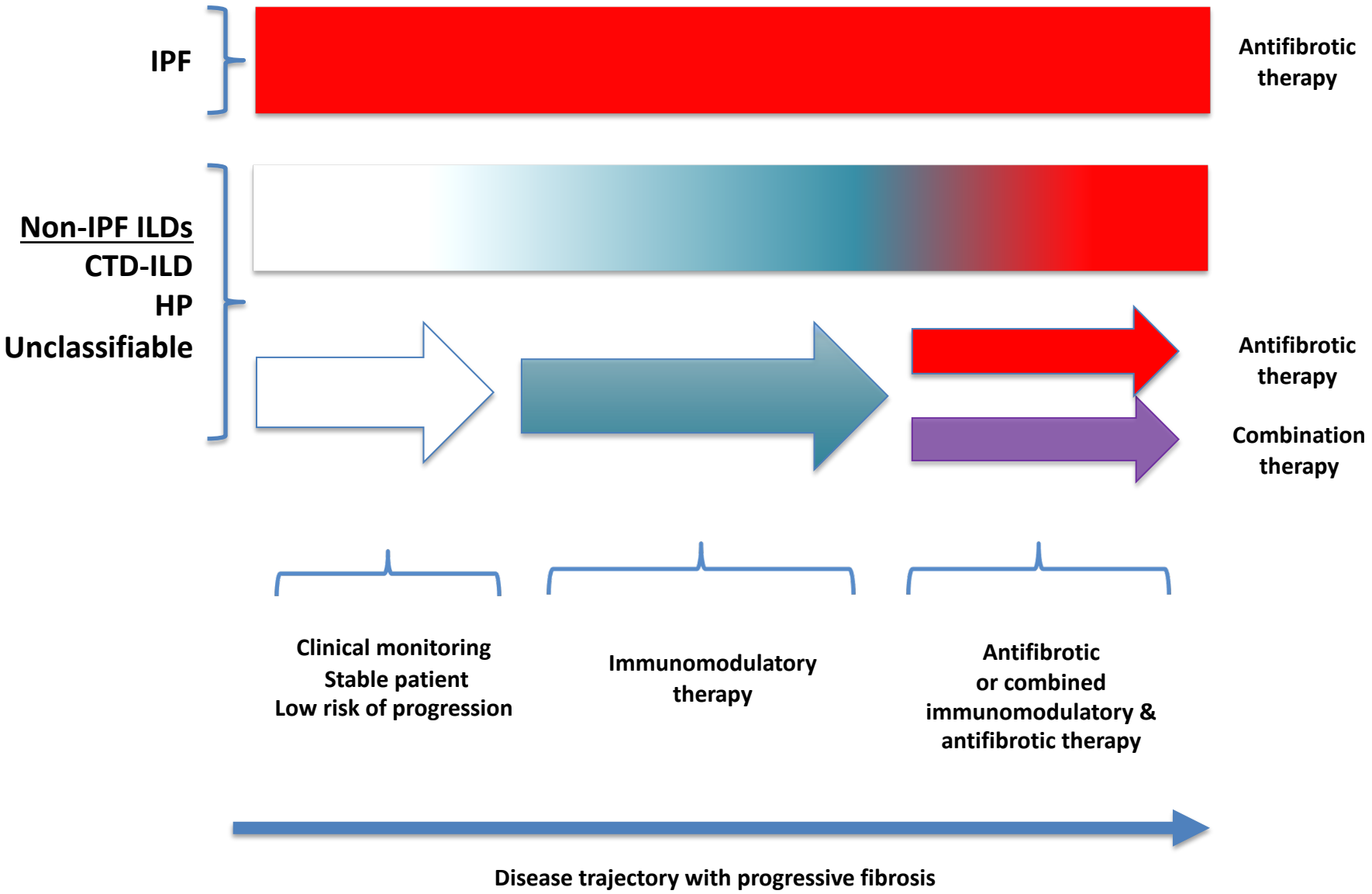
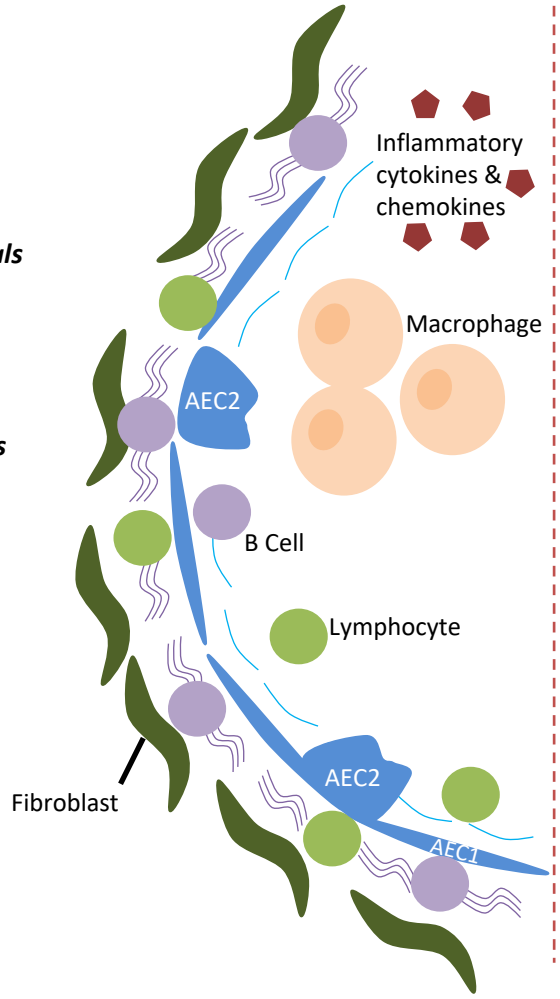
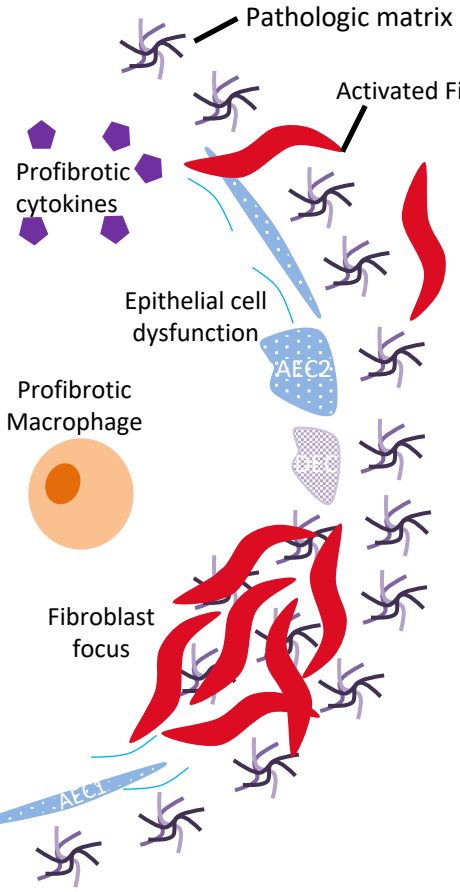

IPF
Antifibrotic therapy
Non-IPF ILDs
CTD-ILD
HP
Unclassifiable
Antifibrotic therapy
Combination therapy
Clinical monitoring
Stable patient
Low risk of progression
Immunomodulatory therapy
Antifibrotic or combined immunomodulatory & antifibrotic therapy
Disease trajectory with progressive fibrosis

## Immunomodulatory

## Fibro-modulatory




***Pathologic Macrophage Signals***
*Tocilizumab*

***Pathologic Lymphocyte Signals***
*Cyclophosphamide*
*Azathioprine*
*Mycophenolate*
*Tofacitinib**
*Abatacept*

***Pathologic B-cell Signals***
*Rituximab*
*Ixazomib**

***Pathologic Epithelial Signals***
*Pamrevlumab*
*PLN-74809**
*Senolytics**

***Pathologic Macrophage Signals***
*Pentraxin 2*
*TRK-250**
*Jaktinib DM**
*TD139**

***Pathologic Mesenchymal Signals***
*Nintedanib?**
*Pirfenidone?**
*TRK-250*
*ND-L02-s0201*
*BMS-986278*
*KD025*
*Setanaxib**
*CC-90001**