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LEADING ARTICLE

Current and Future Treatment Landscape for Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) remains a disease with poor survival. The pathogenesis is complex and encompasses multiple molecular pathways. The first-generation antifibrotics pirfenidone and nintedanib, approved more than 10 years ago, have been shown to reduce the rate of progression, increase the length of life for patients with IPF, and work for other fibrotic lung diseases. In the last two decades, most clinical trials on IPF have failed to meet the primary endpoint and an urgent unmet need remains to identify agents or treatment strategies that can stop disease progression. The pharmacotherapeutic landscape for IPF is moving forward with a number of new drugs currently in clinical development, mostly in phase I and II trials, while only a few phase III trials are running. Since our understanding of IPF pathogenesis is still limited, we should keep focusing our efforts to deeper understand the mechanisms underlying this complex disease and their reflection on clinical phenotypes. This review discusses the key pathogenetic concepts for the development of new antifibrotic agents, presents the newest data on approved therapies, and summarizes new compounds currently in clinical development. Finally, future directions in antifibrotics development are discussed.

Key Points

Idiopathic pulmonary fibrosis (IPF) remains a fatal and incurable disease despite the use of approved antifibrotic drugs.

Development of novel antifibrotics drugs has consistently increased over the last decades, but unsolved issues remain about endpoints, duration, and inclusion/exclusion criteria of future clinical trials.

A better knowledge of mechanisms leading to IPF onset and progress is crucial to the development of new compounds.

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1 Introduction

Idiopathic pulmonary fibrosis (IPF) is an incurable chronic interstitial lung disease (ILD) characterized by irreversible fibrotic destruction of lung architecture. The prevalence of IPF ranges from 20 to 80 patients per 100,000 and the majority of affected patients are male with a positive history of cigarette smoking [1]. Median survival time is 3–5 years after diagnosis without treatment [2], but recently published observations report improving survival over the last 2 decades, may be related to earlier diagnosis, and use of antifibrotics [3, 4].

Pirfenidone and nintedanib were approved worldwide for the treatment of IPF almost 10 years ago. Although they have a different mechanism of action and safety profile, their efficacy in slowing the decline of forced vital capacity (FVC) and reducing mortality risk over time is similar. In advanced IPF stages, transplantation for selected patients and palliative care are needed. Comorbidities and complications negatively impact IPF prognosis, i.e. pulmonary hypertension, lung cancer, and, above all, acute exacerbations, which can occur in 10% of patients per year and are linked to higher mortality within 3 months [5].

The lack of curative treatment has generated research and investments in IPF, but most of the trials, especially those

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in phase II and III, have failed to meet the primary endpoint [2].

The aim of this review was to provide insight into the newest concepts of IPF pathogenesis and illustrate recent advances in pharmacological therapy for IPF, including new data and data on already approved agents.

2 Pathophysiology of Idiopathic Pulmonary Fibrosis (IPF) [and Selected Potential Therapeutic Targets]

Pathologically, IPF is characterized by the excessive production and disorganized deposition of extracellular matrix (ECM) components, which, by progressively replacing the normal lung parenchyma, lead to irreversible architectural distortion and loss of organ function. Although, by definition, IPF is a disease of unknown cause, several risk factors (e.g., cigarette smoking, subclinical infection, environmental pollutants, occupational exposures, chronic microaspiration of gastric content, abnormal composition of the lung microbiota and genetic predisposition), and pathogenic mechanisms have been implicated in its development [6]. Overall, IPF is believed to occur in genetically predisposed individuals (i.e., carriers of telomerase gene mutations or short telomeres) following recurrent alveolar epithelial cell (AEC) injury [7]. In this scenario, an array of cytokines and chemokines released by damaged AECs, and including, among others, tumor necrosis factor (TNF)-α, interleukin (IL)-1, and chemokine (CC-motif) ligand 2 (CCL2), activate residential cells and recruit circulating cells, thus perpetuating alveolar damage. Dysfunctional epithelial and endothelial cells also secrete fibrogenic mediators, such as transforming growth factor (TGF)-β, which induces epithelial-to-mesenchymal transition (EMT) as well as fibroblast recruitment, proliferation, and differentiation to myofibroblasts, the main collagen-producing cells [8]. TGFβ is one of the most potent profibrotic mediators, by inducing collagen synthesis and inhibiting collagen degradation [9]. In addition, TGFβ is an inducer of a plethora of fibrogenic molecules such as connective tissue growth factor (CTGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), and platelet-derived growth factor (PDGF). TGF-β is secreted in an inactive form, with αvβ6 integrin playing a crucial role in its activation [10]. Accordingly, αvβ6 integrin is a potential therapeutic target in IPF [11].

Aging contributes to disease pathogenesis by depleting type 2 AECs, the main progenitor cells in the alveoli, thus impairing the ability of the alveoli to repair injury [12, 13]. Indeed, IPF lung tissue displays several characteristics of aging lungs, such as cellular senescence, telomere shortening, mitochondrial and lysosomal/autophagy dysfunction [14], and epigenetic changes [15].

Fibroblast foci (FF) are clusters of actively proliferating fibroblasts and myofibroblasts that lie in the subepithelial areas of damaged lung. FF are the distinguishing histologic feature of the usual interstitial pneumonia (UIP) pattern of fibrosis, and a high profusion of FF is a marker of poor prognosis in IPF [16]. Compared with normal fibroblasts, fibroblasts isolated from FF display several behavioral differences, including exuberant proliferative potential, excessive contractile capacity, resistance to apoptosis, and distinctive gene expression profile [17]. Mechanical interactions between fibroblasts and the surrounding stiffened ECM provide a positive feedback mechanism that sustains and perpetuates fibroblast activation and collagen synthesis [18]. Four different sources are hypothesized for FF fibroblasts: interstitial fibroblasts, epithelial cells via EMT, fibrocytes, and bone marrow-derived stem cells [19].

3 Therapeutic Challenges

The last decade has witnessed major advances in IPF regarding understanding of disease pathobiology, refinement of diagnostic criteria, and approval of nintedanib and pirfenidone [20]. These advances have fuelled basic translational and clinical research and have led to the identification of several potential therapeutic targets; yet, translating these advances to development of truly efficacious drugs has proven extremely challenging and, thus far, largely unsuccessful. In addition, the approval of nintedanib and pirfenidone has posed new challenges for drug developers and trialists.

3.1 Challenges in Identifying the Right Target

Despite substantial advances in our understanding of disease pathogenesis, the mechanisms involved in IPF development and progression remain elusive and controversial. In addition, although basic and clinical research has identified several potential therapeutic targets, there is no strategy for prioritizing them. Excessive collagen production remains one of the most logical targets in IPF. Indeed, in IPF, progressive fibrosis results from an imbalance between (excessive) synthesis and (reduced) degradation of collagen. Lysyl oxidase (LOX) and LOX-like (LOXL) proteins play a crucial role in ECM remodeling and wound healing by promoting cross-linking and assembly of collagens [21, 22]. Excessive LOXL-2 activity increases the risk for IPF development [23] and progression [24], but allosteric inhibition of LOXL-2 with the monoclonal antibody simtuzumab failed to improve progression-free survival in patients with IPF [25], likely because LOXL-2 is only one of several LOXL enzymes involved in collagen cross-linking. Alternatively, LOXL-2 inhibition may induce paradoxical hyperexpression

of other components of collagen cross-linking or may be ineffective when given in late phases of lung fibrogenesis. Cellular senescence and premature lung aging, telomere shortening, oxidative stress, and mitochondrial dysfunction are additional plausible targets for novel drugs.

Animal models of experimentally induced lung fibrosis are a key element of preclinical drug development [26, 27]. Indeed, a drug that is not effective in animal models is unlikely to move to human studies. However, although animal models have provided important insights into the pathogenesis of pulmonary fibrosis, none of the models developed thus far fully reproduces the progressive nature of IPF or its histologic defining pattern of UIP [28]. Further research on animal models that more closely mimic human disease is warranted.

3.2 Challenges in Patient Selection

The trajectory of IPF progression is variable and unpredictable, with patients displaying slow functional decline over time and others experiencing rapid decline or even episodes of acute clinical worsening [29]. In addition, a significant minority of patients show stable disease, with as many as 15% of patients randomized to placebo in the INPULSIS trial of nintedanib experiencing either no decline or an improvement in FVC percent predicted at the end of the study [30]. Identifying patients at higher risk for rapid decline is critical for prediction of prognosis, management decision making, and design and conductance of clinical trials. In a recent prospective observational cohort, Fainberg and colleagues identified clusters of IPF patients based on lung function (FVC) trajectories by using a two-stage machine learning approach [31]. Specifically, they identified four discrete clusters that were associated with distinct biochemical and clinical features, such as forced expiratory volume in 1 s (FEV_1)/FVC ratio and surfactant protein D (SPD) serum levels. While the existence of clusters of functional decline complicates the interpretation of the study endpoints (particularly if more patients likely to remain stable are randomly assigned to the placebo arm), enriching a trial for patients more likely to progress will greatly improve its efficacy.

3.3 Challenges in Clinical Trial Design

Following the approval of nintedanib and pirfenidone as standard of care (SoC) for IPF, it is unethical to compare new drug candidates with true placebo. An agent could still be tested against placebo in clinical trials restricted to the significant minority of patients who discontinue SoC due to tolerability issues. However, results obtained with this approach may not be generalizable to the broader population of IPF patients, as individuals intolerant to antifibrotic therapy may represent a biologically distinct subset. Currently, novel IPF therapies are evaluated as add-on to background antifibrotic therapy, the rationale being the possibility to target multiple coactivated profibrotic pathways. Intuitively, the best partner drugs are those with complementary, alternative, or synergistic mechanisms of action to SoC. One such example is the preferential phosphodiesterase-4 (PDE-4) inhibitor BI 1015550, which acts synergistically with nintedanib to inhibit mitogen-induced fibroblast proliferation [32].

A debated issue related to clinical trial design is about trial duration. In the last years, the duration of phase II trials in IPF has become 3–6 months, with a limited number of patients per arm. This might be an explanation for the failure of the most recent phase III trials, but the existence of sub-phenotypes of IPF patients and the influence of previous treatments cannot be excluded. Utilization of historical control data or data of the trial population before entering the trial, for instance by looking at functional decline, would be of benefit for the identification of potential predictors of response to antifibrotic treatment [33]

3.4 Challenges in Translating Clinical Trials to Patient Care

With SoC halving the rate of FVC decline compared with placebo, the window to show a further reduction in lung function decline is narrow. In addition, neither nintedanib nor pirfenidone is associated with a consistent improvement in patient-centered outcomes such as symptoms, 6-min walk distance, day-to-day functioning, and fatigue. A recent real-world study has shown that patients with IPF have similar magnitude of response and completion rates to pulmonary rehabilitation compared with patients with COPD [34]. Conversely, in IPF, nonresponse to, and noncompletion of, pulmonary rehabilitation are associated with increased all-cause mortality. These data reinforce both the benefits of pulmonary rehabilitation in patients with IPF and the need for clinical trials assessing a comprehensive therapeutic approach of antifibrotic therapy and pulmonary rehabilitation.

Traditionally, clinical trials of IPF have enrolled patients with mild-to-moderate disease. Although post hoc analyses have suggested that nintedanib [35] and pirfenidone [36] have a similar effect on FVC decline in IPF patients with more versus less severe functional impairment, patients with FVC < 50% or with significant comorbidities such as lung cancer and cardiovascular disease, which are more common in advanced disease [37], are generally excluded from clinical trials. In this regard, the short-term (i.e., 1 year) mortality in clinical trials of IPF is lower compared with the general clinical cohorts [38]. In the future, data from real-life observations and registries should be systematically used to counterbalance the findings from clinical trials, which

generally include overselected patient populations, in an effort to test significant benefits for the primary outcome.

4 Efficacy of the Currently Approved Antifibrotics

IPF has been the subject of many notable clinical trials over the last 2 decades prior to the current era of approved therapies, including both pirfenidone and nintedanib. These included trials of interferon-γ [39] the endothelin receptor antagonists bosentan and macitentan [40–42], warfarin [43], acetylcysteine [44], sildenafil [45], and various immunosuppressive medications [46]. Despite these and other clinical trials failing to identify a viable treatment of IPF, these studies have improved our understanding of IPF biology and clinical trial endpoints. This knowledge was critical for the future success of the currently approved antifibrotics.

4.1 Pirfenidone

Pirfenidone is a small molecule that inhibits fibroblast proliferation and collagen synthesis, likely primarily through regulation of TGFβ [47]. The trials that led to the approval of pirfenidone in IPF showed a benefit on the primary endpoint FVC decline over 1 year [47, 48]. A relative benefit of pirfenidone on the composite endpoint of death or disease progression (driven primarily by FVC), but not on dyspnea or mortality, was observed. Pirfenidone was most frequently associated with gastrointestinal symptoms (primarily nausea) and skin-related events (rash and photosensitivity), which were generally two- to sixfold more common in patients treated with pirfenidone compared with placebo.

Several additional post hoc analyses have suggested consistent effects of pirfenidone in various patient subgroups [49–51]. Efficacy and adverse-effect profiles have further been confirmed in subsequent post hoc analyses and meta-analyses of the major clinical trials [52–58], as well as longer-term, open-label extension studies [36, 59, 60]. Dose reduction, dietary modifications, and skin protection are widely used strategies to manage adverse effects [61, 62].

Pirfenidone has been approved for the treatment of IPF in many countries and is recommended in current clinical practice guidelines for the treatment of mild-to-moderate IPF [63]. Subsequent studies have suggested a similar magnitude of benefit in advanced IPF [64] and a variety of other ILDs when recent progression has been documented [65, 66].

4.2 Nintedanib

Nintedanib is an intracellular tyrosine kinase inhibitor (TKI) with multiple targets involved in lung fibrosis [67]. In the trials that led to the approval of nintedanib in IPF [68], the treatment group showed approximately 50% less decline in FVC compared with placebo. Acute exacerbation was reduced in one trial but not the other, and a trend toward improvement in patients' quality of life, as measured by the St. George's Respiratory Questionnaire (SGRQ), was observed. The INPULSIS trials further confirmed diarrhea as the major adverse effect of nintedanib, affecting about two-thirds of patients, followed by nausea, vomiting, and weight loss. TKIs are likely to induce diarrhea by causing dysfunction in water absorption and secretion in the intestinal lumen, which might be partially mediated by increased activity of the chloride channel CaCC in the luminal membrane of enterocytes [69]. Although colonic CaCC inhibitors have been proposed as a potential therapeutic target for epidermal growth factor receptor (EGFR)-TKI-induced diarrhea [70], nintedanib-associated diarrhea can be effectively controlled with loperamide, an opioid-receptor agonist [71].

Elevated liver enzymes occurred in approximately 5% of nintedanib-treated patients compared with <1% of placebo-treated patients. Overall, approximately 20–25% of patients appeared unable to tolerate nintedanib [71]. Dose reduction to 100 mg twice daily, dietary modification, temporary discontinuation, and rechallenging with a lower dose are widely used strategies to successfully manage adverse effects [71, 72].

Efficacy and adverse-effect profiles have further been confirmed in subsequent post hoc analyses and meta-analyses of the major clinical trials [30, 35, 73–81], as well as longer-term open-label extension studies [82–84].

Based primarily on data from the INPULSIS trials, nintedanib has been approved for the treatment of IPF in many countries and has received a positive recommendation in current clinical practice guidelines for the treatment of mild-to-moderate IPF [63].

4.3 Antifibrotics for Patients with Progressive Pulmonary Fibrosis

Progressive pulmonary fibrosis (PPF) has recently been proposed as a clinical phenotype of patients with ILDs other than IPF who develop a decline in pulmonary function tests (FVC or diffusing lung capacity for carbon monoxide [DLCO]), a worsening of fibrosis at high-resolution computed tomography (HRCT), or symptoms within 1 year [85].

The INBUILD trial explored and successfully proved the efficacy and safety of nintedanib in this patient population [86]. This study and additional post hoc analyses were the basis for the recommendation of nintedanib in this expanded population that includes both IPF and non-IPF forms of PPF [85].

Although pirfenidone showed similar effects as nintedanib on FVC decline over 1 year in the two trials on progressive non-IPF ILD [65, 66], the primary endpoint of the study of pirfenidone in unclassifiable ILD was only met when calculated with FVC values measured at the study center, but not with FVC self-measured by daily home spirometry. In the case of the RELIEF trial, prematurely stopped, only 127 patients were recruited, and, in front of the positive sensitivity analyses, this was the main reason why the recent international clinical practice guidelines did not provide a recommendation for or against pirfenidone in the treatment of PPF [85]. However, after the publication of new meta-analyses [87], showing the consistency of the effect of pirfenidone on FVC decline, national guidelines provided a weak recommendation for the use of pirfenidone in this clinical phenotype [88, 89].

4.4 Combination of Antifibrotics in IPF

An additional uncertainty is the potential combination of nintedanib and pirfenidone given their distinct mechanisms of action and the lack of clear pharmacokinetic interactions [90, 91]. This has been studied in two clinical trials, including one study in which nintedanib was added to pirfenidone [92], and a second study in which pirfenidone was added to nintedanib [93]. Both studies were not powered for efficacy but a potential role for this combination was suggested. Definitive studies are needed to address this question. Based on the paucity of safety and efficacy data and reimbursement issues in most countries, international and national guidelines on IPF treatment recommend the use of antifibrotics combination only within clinical studies [85, 88].

5 New Agents in Clinical Development and Future Perspectives

The majority of past IPF trials did not meet the primary endpoint. Nevertheless, a number of compounds are now under investigation in different trial settings, as add-on therapy or versus true placebo (Table 1).

5.1 Targeting Alveolar Macrophages

5.1.1 Recombinant Human Pentraxin-2 (PRM 151)

Pentraxin-2 (PTX2), a member of the pentraxin protein family, is an endogenous regulator of tissue repair [94]. PTX2 inhibits the differentiation of monocytes into pro-fibrotic macrophages, and fibrocytes inhibit the expression of TGFβ [95, 96]. Circulating levels are decreased in pulmonary, liver, and renal fibrosis. A multicenter, randomized, phase II, double-blind study investigated recombinant human PTX2 (zinpentraxin alfa or PRM-151) in IPF patients [97].

PRM-151 10 mg/kg was administered intravenously every 4 weeks following a three-dose loading regimen. In the treatment group, there was a lesser decline in FVC percent predicted (−2.5) compared with placebo (−4.8) and persisted for up to 52 weeks [97, 98]. About 28% of patients experienced an adverse event, and the cough rate was higher in the treatment arm than placebo [98]. The phase III trial (NCT04552899) evaluating the efficacy and safety of PRM-151 compared with placebo in IPF which has enrolled 665 participants, was prematurely stopped in February 2023 due to futility,

5.2 Targeting Fibroblasts

5.2.1 *GLPG 1690* (Ziritaxestat)

At present, there are several new compounds targeting autotaxin (ATX), an ecto-enzyme [98] that catalyses the hydrolysis of lysophospholipids to the lipid mediator lysophosphatidic acid (LPA; PMID: 3541519). ATX and LPA are elevated in several fibrotic and inflammatory conditions, particularly in serum and bronchoalveolar fluid of patients with IPF (PMID: 3541519). GLPG 1690 is a selective ATX inhibitor [99], and a phase IIa randomized placebo-controlled, 12-week trial (FLORA) showed an improvement in FVC in the treatment group versus placebo. The two identically designed, phase III, randomized clinical trials ISABELA 1 and ISABELA 2 were conducted in 26 countries and recruited a total of 1306 patients with IPF. Patients were randomized 1:1:1 to receive 600 mg of oral ziritaxestat, 200 mg of ziritaxestat, or placebo once daily in addition to SoC for at least 52 weeks [99]. Due to the benefit-to-risk profile of ziritaxestat, the trials were terminated early. Ziritaxestat did not improve the annual rate of FVC decline versus placebo in either study and no benefit for the key secondary outcomes was observed. Moreover, a slightly increased all-cause mortality rate was observed with ziritaxestat compared with placebo in both trials (8–9% vs. 5%).

5.2.2 BMS-986278 and BMS-986020

BMS-986278 is an LPA receptor 1 (LPA1) antagonist currently in phase II development in patients with IPF and progressing fibrosing non-IPF ILD [100]. Patients in both cohorts will be randomized 1:1:1 to receive 30 or 60 mg of BMS-986278, or placebo, administered orally twice daily for 26 weeks in the placebo-controlled treatment period. The primary endpoint is rate of change in FVC percent predicted from baseline to week 26.

Table 1 Novel therapies in IPF patients: selected clinical trials and major findings

Drug/mechanism of action	Trial acronym/NCT no.	Year of completion (reference)	Phase/duration	Efficacy/safety	Next developments
PRM 151 (recombinant human PTX2 protein)	NCT02550873	2018 and 2019 [97, 98]	Phase II/28-week RCT + 76-week open-label crossover extension	Reduction of FVC percent predicted decline and 6MWD/no significant adverse effects	Phase III trial, prematurely stopped (STARSCAPE; NCT04552899)
GLPG 1690 (autotaxin inhibitor)	FLORA/NCT02738801	2018 [99]	Phase II/12-week RCT	Improvement in FVC in the treatment group compared with placebo No difference in safety compared with the placebo group	Twin phase III trials: NCT03711162 (ISABELA-1) and NCT037334442 (ISABELA 2), both prematurely stopped
BMS-986020 (LPA receptor-1 antagonist)	NCT01766817	2018 [101]	Phase II/26-week RCT	Reduction in FVC decline in the treatment group compared with placebo. Hepatobiliary SAE (early termination of study)	No information on further trials available
BMS-986278 (LPA receptor-1 antagonist)	NCT04308681	Ongoing	Phase II/26-week RCT + optional 26-week active-treatment extension period	Results awaited	No information on further trials available
Pamrevlumab (recombinant anti-CTGF mAb)	PRAISE/NCT01890265	2020 [104]	Phase II/48-week RCT	Reduction in FVC decline at 48 weeks seen in the treatment group compared with placebo. No significant adverse effects seen with pamrevlumab	Phase III trials in IPF and PF-ILD ZEPHYRUS I and II (NCT03955146 and NCT04110558 respectively) prematurely stopped
BI 1015550 (PDE-4B inhibitor)	NCT04419506	2022 [107]	Phase II/12-week RCT	Reduction in FVC decline in the treatment group, regardless of background antifibrotics. GI-related symptoms in the BI 1015550 group, especially in those taking antifibrotics	Phase III trial in IPF and PF-ILD in the recruiting phase (FIBRONEER, NCT05321069)
PBI-4050 (G-protein receptor analog)	NCT02538536	2019 [109]	Phase II, 12-week, single-arm, open-label study	FVC stability at week 12 in PBI-4050, and combination PBI and nintedanib Pharmacokinetic issues when combined with pirfenidone	Phase III trial planned
PLN-74809 (integrins αvβ6 and αvβ1 inhibitor)	INTEGRIS-IPF/ NCT04396756	2023, only abstracts available	Phase II, 12-week RCT	Preliminary results: reduction in FVC decline seen in the PLN-74809 group in a dose-dependent way. No significant SAE noted with PLN-74809	Extension of trial planned (NCT04396756)
AP01 (aerosolized pirfenidone)	ACTRN12618001838202 (New Zealand trials registry)	2023 [120]	Phase Ib/24-week, randomized, open-label trial	Mean FVC percent predicted remained stable in the 100 mg twice-daily group Adverse effects less frequent with AP01 than with oral pirfenidone in other clinical trials	Phase III trial planned
TD139 (Inhaled galectin 3 inhibitor)	NCT02257177	2021 [122]	Phase I/IIa/2-week RCT	Inhaled TD139 safe and well tolerated in healthy subjects and IPF patients	Phase IIb study ongoing (GALACTIC-1, NCT03832946)
PA101 (inhaled sodium cromoglycate)	NCT02412020	2017 [124]	Proof-of-concept 2-week RCT	Day-time cough reduction in IPF at day 14 in the treatment group compared with the placebo group. No SAE observed	A phase IIb trial (SCENIC) was terminated in 2020 (NCT03864328)

Table 1 (continued)

Drug/mechanism of action	Trial acronym/NCT no.	Year of completion (reference)	Phase/duration	Efficacy/safety	Next developments
TRK250 (siRNA-based oligonucleotide)	NCT03727802	Ongoing	Phase I/4-week RCT	Results awaited	No information on further trials is available
Treprostinil (inhaled form of PDE-5 inhibitor)	INCREASE/ NCT02630316	2021 [129–131]	Phase III/16-week RCT	Improved 6MWD in the treatment group compared with placebo. Adverse events in the treatment group: cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea	A phase III trial with treprostinil is ongoing (NCT04708782)
Dasatinib/quercetin (tyrosine kinase inhibitor/flavonoid, senolytic effect)	NCT02874989	2019 [118]	Pilot, 3-week, open-label study	Improvement in 6-min walk distance but no improvement in FVC Most common adverse effects were skin irritation and GI discomfort	No information on further trials is available

CTGF connective tissue growth factor, *FCV* forced vital capacity, *GI* gastrointestinal, *IPF* idiopathic pulmonary fibrosis, *mAb* monoclonal antibody, *NCT* National Clinical Trial, *6MWD* 6-min walking distance, *LPA* lysophosphatidic acid, *PDE* phosphodiesterase, *PF-ILD* progressive fibrosing interstitial lung disease, *PTX2* pentraxin-2, *SAE* serious adverse event, *siRNA* small-interfering RNA, *RCT* randomized controlled trial

A phase II trial with another LPA1 antagonist (BMS-986020), despite a significant reduction in the rate of FVC decline between the placebo and twice-daily dosage group, was terminated early due to hepatobiliary toxicity [101].

5.2.3 Anti-Connective Tissue Growth Factor-Monoclonal Antibody (Pamrevlumab)

CTGF modulates myofibroblast activation, ECM deposition, and fibrotic remodeling via TGFβ downstream signaling [102, 103]. In the PRAISE phase II trial, the recombinant human antibody pamrevlumab administered intravenously consistently reduced the decline in the percentage of predicted FVC by 60.3% at week 48 (mean change from baseline −2.9% with pamrevlumab vs. −7.2% with placebo, with a between-group difference of 4.3%; $p = 0.033$) [104]. The treatment effect was corroborated by the improvement of radiology (quantitative lung fibrosis score at HRCT) and symptoms (SGRQ score). Due to the relatively low number of patients included ($N = 103$), and since background antifibrotics were not permitted, the results should be treated with caution. A phase III program consisting of two identical trials (ZEPHYRUS I and II) (NCT03955146 and NCT04419558) was prematurely stopped in June 2023 since the ZEPHYRUS I study did not meet the primary endpoint (press release link: https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-announces-topline-results-phase-3-zephyrus-1-study).

5.2.4 Preferential Phosphodiesterase-4B Inhibitor (BI 1015550)

Phosphodiesterases (PDEs) are the principal superfamily of enzymes responsible for degrading the secondary messengers 3′,5′-cyclic nucleotides cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Inhibiting this pathway leads to a decrease in levels of prostaglandin E2, which regulates essential functions of fibroblasts [105]. BI 1015550 appears to also inhibit TGFβ1-induced myofibroblast transformation and ECM deposition [32, 106]. Based on preclinical models, the selectivity for PDE-4B is associated with fewer gastrointestinal adverse effects [106]. In a double-blind, placebo-controlled, parallel-design, phase II trial, patients were randomly assigned in a 2:1 ratio to receive either BI 1015550 18 mg twice daily or placebo, administered orally, for 12 weeks. The primary endpoint was a change in baseline FVC at week 12 and patients were stratified according to background antifibrotic treatment (PMID: 35569036). Bayesian analysis was used to calculate the probabilities that BI 1015550 was superior to placebo in each group. Patients in the BI 1015550 arm, both with and without pre-existing antifibrotic use, had a lower median change, or even a slight improvement, in FVC at 12

weeks compared with those in the placebo group (median difference 62–84 mL). A mixed model with repeated measures (MMRM) analysis provided results that were consistent with those of the Bayesian analysis. Diarrhea was the most common adverse effect leading to discontinuation in 13 patients, almost all of whom were taking antifibrotics [107]. FIBRONEER™ is a currently recruiting phase III program initiated globally to evaluate BI 1015550 in IPF and other progressive fibrosing ILDs (NCT05321069 and NCT05321082, respectively).

5.2.5 PBI-4050

By binding G protein-coupled receptors GPR40 and GPR84, PBI-4050, an orally active synthetic analog of a medium-chain fatty acid, reduces fibrosis via the regulation of multiple antifibrotic pathways [108]. PBI-4050 inhibits the differentiation of fibroblasts to myofibroblasts, and reduces accumulation of ECM protein deposition and fibrosis.

In the phase II, open-label trial of PBI-4050 in IPF, besides a good safety profile, no significant changes in FVC, either in percent predicted or milliliters, from baseline to week 12 were observed for PBI-4050 alone or PBI-4050 + nintedanib, but not in combination with pirfenidone [109]. The results should be interpreted with caution since the trial had no placebo control group.

5.3 Targeting Epithelial Cells

PLN-74809, an oral small molecule inhibitor of integrins αvβ6 and αvβ1, suppresses TGFβ in fibrotic lung tissue and potentially reduces systemic adverse effects in the treatment of IPF [110]. PLN-74809 INTEGRIS-IPF is an ongoing, phase IIa, open, randomized, double-blind, dose-ranging (60–320 mg), placebo-controlled study evaluating the safety, tolerability, and pharmacokinetics of this compound in IPF patients. The average decline in FVC for patients receiving placebo was 74.1 mL, and 15.1 mL for all patients taking PLN-74809, with a dose-dependent effect. A similar trend was observed for the quantitative HRCT lung fibrosis score [111].

5.4 Senotherapy for IPF

Senolytics can selectively induce the death of senescent cells by selective apoptosis in senescent cells, with the potential to prevent onset of age-related diseases [112]. Since senescence is driven by chronic oxidative stress, antioxidants, including novel molecules and mammalian target of rapamycin (mTOR) signaling inhibitors, might be used as senostatics [113, 114]. The flexible nature of senolytics could have great potential to promote healthy immune function in aging populations.

An open-label pilot study investigated the combination of dasatinib, a TKI, and quercetin, a flavonoid, both having senolytic effects in vitro in human and murine cells [115–117], in patients with IPF. The study had a small sample size ($N = 14$) and demonstrated a significant improvement in the 6-min walk distance ($p < 0.05$), but no improvements in the FVC, frailty index (FI-LAB), and reported health. The most common adverse effects were skin irritation and gastrointestinal discomfort [118]. Further studies with senolytics in pulmonary fibrosis are warranted.

5.5 New Perspectives on Inhaled Treatment

Delivering drugs directly to the alveolar space has the potential to achieve higher concentrations in the lung and to reduce systemic effects.

A phase I, randomized, double-blinded, placebo-controlled, dose-escalation study investigated the safety and pharmacokinetics of a single administration of an aqueous formulation of pirfenidone delivered by a high-efficiency vibrating plate nebulizer [119]. Aerosolized pirfenidone was well tolerated in healthy volunteers, smokers, and IPF patients. Interestingly, the nebulizer dose averaged a 15-fold lower systemic pirfenidone exposure than reported with oral administration of the licensed oral dose [119]. A phase I/II clinical study of two dose regimens of AP01 (a formulation of pirfenidone optimized for delivery via inhalation) recruited 91 IPF patients, randomly assigned to 50 mg once daily or 100 mg twice daily. Adverse effects, with cough being the most frequent adverse effect, were less frequent with AP01 than with oral pirfenidone in other clinical trials. Mean FVC percent predicted remained stable in the 100 mg twice daily group [120]. A phase III program in IPF and PPF is planned.

Inhaled *N*-acetylcysteine, combined with oral pirfenidone, did not result in substantial benefits for IPF patients in a recently published phase II trial [121].

The efficacy of inhalational TD139, a small molecule inhibiting Gal-3, a member of the β-galactoside-binding lectins family, which regulates fibrotic processes and is overexpressed in the BAL fluid of patients with IPF, was evaluated through a randomized controlled, phase I/IIa dose-ascending trial. Sixty participants were recruited, 24 of whom were diagnosed with IPF [122]. TD139 was well-tolerated by both healthy and IPF patients: taste disturbance (36.1%) and cough (11.1%) were the most common adverse effects [122]. A phase II trial in IPF for efficacy evaluation is ongoing (NCT03832946).

TRK250, previously known as BNC-1021, inhibits the transcription of TGFβ1 by producing silencing RNA (siRNA) targeting TGFβ1 messenger RNA (mRNA). TRK250 has demonstrated its ability to reduce the expression of TGFβ1 and collagen production in the lungs in animal models [123]. A phase I, placebo-controlled, double-blind, randomized study

assessing the safety and tolerability of single and multiple inhaled doses of TRK250 in subjects with IPF for 4 weeks was completed in April 2022 (NCT03727802). The results of that study are yet to be released.

Older formulations of sodium cromoglycate are approved for the treatment of asthma. PA101 is a novel formulation that was tested in IPF patients for 2 weeks and compared with placebo. There was a mean reduction in daytime cough frequency at day 14 (31.1%) when adjusted for the placebo [124]. Another phase IIb trial (SCENIC) that investigated varying doses of inhaled sodium cromoglycate over 12 weeks in IPF patients found no benefit in reducing cough [125].

In the last two decades, PDE-5 inhibitors have raised interest as a potential treatment for IPF, whereas discordant effects were observed for sildenafil, an oral PDE-5 inhibitor and pulmonary vasodilator, in patients with IPF [45, 126–128].

The INCREASE trial, which investigated treprostinil, an inhaled form of PDE-5 inhibitor, in IPF and non-IPF ILD with pulmonary hypertension, found a significant improvement in the mean FVC at 16 weeks compared with placebo [129]. A post hoc analysis of 326 patients (inhaled treprostinil, $n = 163$; placebo, $n = 163$) assessed the effect of continued treatment with inhaled treprostinil on multiple disease progression events, defined as a 15% or more decline in 6-min walk distance, a 10% or more decline in FVC, acute exacerbation, cardiopulmonary hospitalization, lung transplantation, or death. Patients who received inhaled treprostinil were significantly less likely to experience further disease progression events after an initial event, compared with patients receiving placebo [130].

6 Conclusion

Thus far, most clinical trials in IPF have failed to meet the primary endpoint. Aside from reasons related to clinical trial design, duration, and heterogeneity of included populations, we must consider that we are examining short-term intervention effects of new drugs. Moreover, our understanding of IPF pathogenesis is still limited and we should keep focusing our efforts to deeper understand the mechanisms underlying this complex disease and their reflection on clinical phenotypes.

Declarations

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