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REVIEW

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Promising advances in treatments for the management of idiopathic pulmonary fibrosis

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ABSTRACT

Introduction: Following the INPULSIS and ASCEND studies, leading to the first two approved antifibrotic therapies for patients with IPF, ongoing investigations are firmly exploring novel agents for a targeted effective and better tolerated therapy able to improve the natural history of the disease.

Areas covered: This review aims to analyze recent advances in pharmacological research of IPF, discussing the currently available treatments and the novel drugs under investigation in phase 3 trials, with particular emphasis on BI 1015550 and inhaled treprostinil. The literature search utilized Medline and Clinicaltrials.org databases. Critical aspects of clinical trial design in IPF are discussed in light of recently completed phase III studies.

Expert opinion: While randomized clinical trials in IPF are currently underway, future objectives should explore potential synergistic benefits when combining novel molecules with the existing therapies and identify more specific molecular targets. Moreover, refining the study design represent another crucial goal. The aim of the pharmacological research will be not only stabilizing but also potentially reversing the fibrotic changes in IPF.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) represents a chronic respiratory condition of uncertain origin defined for the thickening and stiffening of lung tissue with abnormal accumulation of fibrosis. This leads to reduced lung function, progressive shortness of breath, and irreversible damage to lung structure, ultimately resulting in respiratory failure. The incidence ranges from 1 to 14 cases per 100,000 individuals, with a prevalence of 3–45 cases per 100,000 [1]. Various aspects, including location and age, influence the impact of IPF, with a notable rise observed in older groups. An identifiable pattern of usual interstitial pneumonia (UIP) can be observed through high-resolution computed tomography (HRCT) or surgical lung biopsy.

The precise triggers of the fibrotic mechanisms remain unclear, and current knowledge is primarily supported by studies involving animal models of pulmonary fibrosis. Genetic mutations, particularly involving TERC and MUC5B genes, are considered as contributors to IPF [2]. Senescent alveolar epithelial cells and fibroblasts emerge as a key factor in promoting scar tissue, but the exact processes remain unknown [3,4].

Recent observations suggest that repetitive micro-damages to alveolar type II cells (ATII) may support an abnormal mesenchymal-epithelial engagement in susceptible subjects [5]. Growth factors and profibrotic molecules released from ATII cells cause the recruitment of inflammatory cells, fibroblast proliferation and/or activation into myofibroblasts. The resulting 'fibrotic foci' become sources of collagen accumulation, distorting lung architecture [6,7]. Additionally, evidence demonstrates that ATII cells could transdifferentiate in metaplastic basal cells following in response to fibrogenic signaling [8].

The progress of lung fibrosis is sustained by the relationship between injured alveolar ATII cells and various mediators [2]. Profibrotic mediators include transforming growth factor β (TGF-β), interleukin 13 (IL-13), connective tissue growth factor (CTGF), insulin-like growth factor 1 (IGF-1), fibroblast growth factor 2 (FGF-2), and platelet-derived growth factor (PDGF). Others play an antifibrogenic role [2,4,9–11]. Moreover, studies using in vitro models and animal subjects have highlighted the crucial role of receptor tyrosine kinases (RTKs), such as FGF receptor (FGFR), vascular endothelial growth factor receptor (VEGF-R), and PDGF receptor (PDGF-R), as well as non-receptor TK, for the fibroblast stimulation and extracellular matrix (ECM) production [6].

Median survival rates have been described to vary from 2 to 5 years [12], and untreated patients typically experience a decline in forced vital capacity (FVC) of 150–200 mL per year, based on data from the placebo arm of randomized clinical trials (RCTs) [13]. The trajectory of IPF is incalculable and driven by several factors, for example the rate of exacerbations and/or progression, and the presence of other systemic diseases.

2. Pharmacological research

Nintedanib and pirfenidone have emerged in the last years as the two initial antifibrotic approaches able to slow the decline

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Article highlights

- The currently approved antifibrotic drugs in IPF, nintedanib and pirfenidone, are capable of slowing the fibrotic processes but cannot stop the progression completely, often leading to side effects.
- Research into new therapeutic approaches in IPF is crucial given novel insights into the pathogenesis of the disease.
- Pharmacological studies face various challenges, and notable failures were encountered in recent Phase III clinical trials, such as the GALAPAGOS ISABELA 1 and 2 studies, STARSCAPE trial and ZEPHYRUS I trial.
- The eligibility criteria and the study endpoints commonly adopted in RCTs on IPF may have limitations.
- Additional research is required to explore the potential synergistic benefits of novel drugs added to existing approved therapies.

in pulmonary capacity and improve disease outcomes [14–16]. Historically, treatment involved the use of anti-inflammatory and immunosuppressive drugs. However, the pharmacological triple combination of azathioprine, steroids and N-Acetylcysteine has been avoided since the unfavorable clinical outcomes revealed from the PANTHER trial [17].

Research into innovative therapeutic strategies in IPF is imperative since the current medications are not capable of reversing the fibrotic process. Unfortunately, almost 20% of participants undergoing pirfenidone or nintedanib therapy in RCTs required the interruption of the drug because of adverse events. Early discontinuation was experienced in 20.6% of patients in RCTs evaluating nintedanib in IPF [18–20]. Similarly, a phase 3 clinical trial evaluating pirfenidone found that approximately 12% of IPF patients had to discontinue the study medication due to adverse events (AEs) [21,22]. These findings have been substantiated in real-world studies, emphasizing the necessity to explore drugs with enhanced efficacy and tolerability.

This work aims to describe novel insights in pharmacological research in IPF. We explore the currently available treatments, then the novel drugs evaluated in phase 3 clinical trials, highlighting their potential impact on the clinical management of individuals with IPF. We also focus on the outstanding failures of some recent phase 3 RTCs and the future challenges.

3. Existing antifibrotic medications

The approval of pirfenidone and nintedanib as viable treatments comes from the data of the ASCEND and the INPULSIS trials, respectively. Both drugs were approved from the US Food and Drug Administration (FDA) in 2014, while have been validated by the European Medicines Agency (EMA) since 2011 and 2015, respectively. The latest clinical practice guidelines from ATS/ERS/JRS/ALAT have issued a conditional recommendation endorsing their use in the management of patients affected by IPF [23].

3.1. PFD

Pirfenidone (PFD) is an oral agent currently approved as antifibrotic therapy for patients with IPF and conditionally recommended in international treatment guidelines, prescribed at a total dose of 2.403 mg daily. The drug is able to slow the disease progression, modulating inflammatory and fibrotic processes, despite the precise biological effect is not completely understood [24]. In phase III studies, pirfenidone resulted effective in reducing the rate of absolute decline in percent predicted FVC. Particularly, in the ASCEND study, leading to FDA approval, treatment with pirfenidone showed a reduction in the annual rate of FVC decline by 116 mL. Specifically, the treatment group exhibited a decline of −164 mL, whereas the placebo group showed a decline of −208 mL [25]. Additionally, PFD lowered the proportion of IPF participants experiencing an FVC decline of ≥10% by almost 48%, compared to the placebo arm. According to pooled analysis of the phase 3 trials, pirfenidone reduced all-cause mortality, IPF-specific mortality, and respiratory-related hospital admissions [25,26].

Interestingly, there is a notable difference in therapeutic dosages between Asia and the West. In a phase III clinical trial, Japanese patients were given a low dose of pirfenidone (1200 mg/day), instead of the standard dose of the drug (2403 mg/day), which also resulted in a significantly slower decline in FVC compared to the placebo group [27]. Another post-marketing surveillance study, investigating the role of PFD in advanced IPF within a real-world setting, considered a lower dosage (up to 1800 mg/day) used in Korean patients to demonstrate both well-tolerability and a significant therapeutic effect of PFD regardless of IPF severity [28].

The most frequent adverse events of PFD include rash, photosensitivity reaction and gastrointestinal effects, with a cessation rate of 14.4% and 15% in the ASCEND and the CAPACITY trials, respectively [21,25]. Aerosol administration could improve efficacy and safety of the drug by enhancing delivery to lung tissue and limiting systemic exposure. Based on this premise, the phase 1b randomized open-label ATLAS study recently explored the inhaled formulation of pirfenidone (AP01) in a study population of 91 IPF patients. This trial demonstrated a stable mean FVC % predicted and a lower incidence of systemic AEs compared to the oral formulation [29].

3.2. Nintedanib

Nintedanib is a tyrosine kinase inhibitor that blocks several mechanisms involved into the initiation and progression of pulmonary fibrosis, such as the proliferation and activation of pulmonary fibroblasts and the deposition of extracellular matrix [30]. The efficacy and safety of nintedanib have been explored in different RTCs. The last two phase III trials (INPULSIS) enrolled over 1000 patient with IPF, demonstrating a significant reduction in the rate of FVC decline compared to placebo [18]. Diarrhea was the most common adverse evented reported in RCTs, affected nearly 62% of treated patients compared to 18% in the placebo group. According to pharmacovigilance studies, diarrhea was less commonly described although it is the most frequent AE (301.6 events per 1000 patient-years) [31]. The frequency of dose reduction or interruption due to gastrointestinal events resulted similar [32,33]. Since the interaction with P-glycoprotein and CYP3A4 inhibitors or inducers, nintedanib can also increase the rate of bleeding in patients receiving anticoagulants [34].

Preliminary results of phase 1 trial of inhaled nintedanib (AP02) were reported last year, enrolling 32 healthy volunteers and 6 IPF patients. The results revealed better tolerability for the inhaled formulation with no serious AEs (SAEs) [35].

A study of Wijsenbeek et al. has recently described the role of nintedanib in controlling respiratory symptoms and fibrosis progression in patients with progressive pulmonary fibrosis, based on changes in Living with Pulmonary Fibrosis (L-PF) questionnaire over 52 weeks observed in the INBUILD trial. It was found that nintedanib can mitigate the clinical deterioration of dyspnea, cough and overall quality of life, given that only a smaller proportions of participants in the treatment arm reported a significant worsening of symptoms over 52 weeks [36]. Additionally, a systematic review and meta-analysis found that antifibrotic treatment may be linked to a reduced risk of acute exacerbation in IPF, especially with nintedanib, while the effects of pirfenidone use seemed less pronounced. The underlying mechanisms are unclear [16].

3.3. Evidence on nintedanib plus pirfenidone

The combined use of nintedanib and pirfenidone, regulating several biological pathways of lung fibrosis, could have an additive or synergistic effect in patients with IPF. However, AEs may be increased in such cases. In vitro evidence suggests that the combination of the two antifibrotic agents can reduce proliferation of fibroblastic cells with a dose dependent effect, modulating the ultrastructure and activity of fibroblasts and myofibroblasts [37]. Based on a recent systematic review and meta-analysis [38], only one trial directly evaluated efficacy and safety of the combination therapy compared to nintedanib alone in IPF. This exploratory open-label study (INJOURNEY Trial, NCT02579603) randomized 105 patients with IPF and FVC higher or equal to 50% predicted for 12 weeks of treatment [39]. The primary endpoint was the percentage of participants with gastrointestinal AEs, that were described in approximately 70% of patients treated with combination therapy and 52% of those with nintedanib alone. Two-thirds of participants fully completed the 12-week treatment period with both agents, while one-third prematurely interrupted pirfenidone. The mean changes in FVC were −13.3 mL and −40.9 mL in the combination treatment arm compared to nintedanib alone, respectively [39]. Future larger RCTs will be essential to better understand the potential efficacy of a combination of antifibrotic drugs in IPF.

4. Exploring novel approaches

Pharmacological research has intensified in the pursuit of innovative therapeutic agents for the treatment of IPF. The current antifibrotic drugs are capable of slowing disease progression but cannot halt the progression completely, and often lead to gastrointestinal side effects. In the current therapeutic landscape, there is a shift toward better targeted molecules, in contrast to the larger effects of existing therapies, with a potential for combination therapy.

The ongoing exploration of novel treatments (Table 1) emphasizes the need to address knowledge gaps, including the phenotyping of IPF patients, particularly based on genetic markers. These advancements hold the promise of refining treatment approaches and improving outcomes for individuals affected by IPF.

5. Phase 3 clinical studies

5.1. Ziritaxestat

Ziritaxestat, also known as GLPG-1690, is a first-in-class small molecule that selectively inhibits the enzyme autotaxin (ATX). Preliminary data show that the autotaxin activity, primarily inducing the production of lysophosphatidic acid, is enhanced in IPF [40], proving their role in disease pathogenesis.

Following a phase I study, where GLPG-1690 was well tolerated and associated with a maximum reduction in plasma lysophosphatidic acid (LPA) levels of around 90% [41], the drug was investigated in the phase II FLORA study with

Table 1. Novel study compounds with different routes of administration for patients with IPF.

Drug	Route of administration	Phase of development/NCT	Biological effects	Common side effects
BI 1,015,550	Oral	Phase 3; NCT05321069-NCT05321082	Preferential inhibitor of PDE4B, expressed in inflammatory cells that specifically degrades cAMP.	Gastrointestinal (nausea, diarrhea), fatigue.
Treprostinil	Inhalation	Phase 3; NCT04708782	Decreasing recruitment of fibrocytes and fibroblast activity, promoting direct vasodilation of pulmonary and systemic arterial vascular beds, inhibiting platelet aggregation.	Cough, headache, dyspnea, dizziness, nausea, fatigue, diarrhea.
BMS-986278	Oral	Phase 2; NCT04308681	LPA1 antagonist. LPA1 appears overexpressed in lung fibrosis causing fibroblast recruitment and resistance to apoptosis.	Diarrhea, cough, orthostatic hypotension.
Bexotegrast (PLN-74809)	Oral	Phase 2a; NCT04396756	Blocking both the integrins $\alpha_v\beta_1$ and $\alpha_v\beta_6$, cell-surface proteins, which are key mediators of the activation of the profibrotic TGF-β.	Headache, nausea, dizziness.
Olitigaltin (GB0139)	Inhalation	Phase 2b; NCT03832946	Inhaled galectin-3 inhibitor. Galectin has a profibrotic role interacting with integrins and growth factor receptors.	Dysgeusia, cough.
Ianalumab (VAY736)	Injection	Phase 2; NCT03287414	Monoclonal antibody against BAFF-R	Local injection site reaction, infections, blood and lymphatic disorders.
TAS-115	Oral	Exploratory Phase 2	Inhibitory effect on PDGF-R and VEGF-R, blocking the proliferation and migration of fibroblasts.	Rash and eyelid oedema

Abbreviations: BAFF-R, B-cell activating factor receptor; cAMP, cyclic adenosine monophosphate; CTGF, connective tissue growth factor; LPA, lysophosphatidic acid; NCT, national clinical trial number; PDE4B, phosphodiesterase 4B; PDGF-R, platelet-derived growth factor receptor; TGF-β, transforming growth factor β; VEGF-R, vascular endothelial growth factor receptor.

promising findings on efficacy and safety in patients with IPF [42]. The mean change in FVC from baseline to week 12 was 25 mL in treatment arm vs −70 mL in placebo group.

The subsequent phase 3 trials, called GALAPAGOS ISABELA 1 and 2 (NCT03711162 and NCT03733444), starting in 2018, enrolled 1306 participants suffering from IPF treated with GLPG1690 600 or 200 mg (in addition to local standard of care) or placebo for at least 52 weeks [43]. The primary endpoint was the rate of FVC decline, while secondary endpoints included composite endpoint of disease progression or all-cause mortality and time to first hospitalization due to respiratory causes. However, the two study were halted in advance since the elevated rate of IPF progression and mortality in patients treated with GLPG-1690. Moreover, the FVC decline was not significantly reduced compared to placebo, differently from the results from the FLORA study. Other future investigations into different autotaxin inhibitors will contribute valuable insights into the factors underlying the ISABELA trials' limitations.

5.2. Zinpentraxin alfa

Zinpentraxin alfa (rhPTX-2), previously called PRM-151, is a recombinant form of the human pentraxin-2 and it is characterized by an antifibrotic activity. Specifically, pentraxin-2 May modulate the innate immune system via the inhibition of monocyte differentiation into macrophages, the reduction of TGF-β levels, and stopping the transition from monocytes to fibrocytes [38–40]. Patients affected by IPF showed lower blood levels of PTX-2, with a reduction potentially correlated with the severity of the lung fibrosis [44].

The intravenous (IV) infusion of zinpentraxin alfa in IPF was initially investigated in the PRM-151–202 study, phase 2 clinical trial (NCT02550873) that proved a significant efficacy compared to placebo on lung function evaluating the mean FVC decline and the 6-minute walk distance (6MWD) over 28 weeks, other than a good tolerability [45]. Therefore, these results and the subsequent open-label extension (OLE) provided the rationale for the following phase III STARSCAPE program (NCT: NCT04552899) and its related OLE study (NCT04594707).

Thus, the 52-week phase 3 RCT STARSCAPE investigated the efficacy and safety of zinpentraxin alfa in patients with IPF, however, it was interrupted early for a failed futility analysis that described no benefit over placebo [46]. The study enrolled 664 patients with a documented diagnosis of IPF, from March 2021 to February 2023, and a total of 106 patients (16%) completed the trial. The primary endpoint was the absolute change from baseline to Week 52 in FVC but there was no significant difference between treatment (−235.72 mL) and placebo group (−214.89 mL; $p = 0.5420$). Also, the secondary endpoints of the absolute change in %FVC and the 6MWTD were not met. Zinpentraxin was generally well tolerated. Almost 72% and 74% of participants receiving placebo and investigational drug, respectively, had at least one AE, but no difference ≥ 2% in terms of AEs incidence was observed between the two arms. To conclude, zinpentraxin alfa was safe but no clinical benefit was demonstrated compared to placebo.

5.3. Antibiotics

An alteration of the pulmonary microbial balance, meant like an increased bacterial load and/or reduced heterogeneity, may raise the risk of development and progression of lung fibrosis [47–49]. Thus, pulmonary microbiome can be modulated by a chronic antimicrobial treatment, representing a potential treatable cause. Based on these data, a phase 3 RCT trial (EME-TIPAC, ISRCTN17464641) evaluated the efficacy of co-trimoxazole in patients with moderate and severe IPF, enrolling 342 participants randomized to receive oral co-trimoxazole or placebo between 2015 and 2018. The treatment period was at least of 12 months, with a maximum of 42 months [50]. Unfortunately, there were not statistically differences among the two groups for the composite endpoint that included time to death (all causes), lung transplant, or first nonelective hospital admission for any cause.

Following the EME-TIPAC trial, the CleanUP-IPF study (NCT02759120) investigated the combination of antimicrobials plus conventional antifibrotics in comparison to usual care in IPF [51]. This trial randomized 513 IPF patients from 2017 to 2020 (all enrolled participants were included in the analysis) but was terminated for futility in December 2019. Antimicrobials included co-trimoxazole or doxycycline. The main outcome was time to first nonelective hospitalization due to pulmonary condition or all-cause mortality. No significant difference was observed between the two arms, since 52 primary endpoint events occurred in the standard care in combination with antibiotics group and 56 events in the usual care group (adjusted HR, 1.04; P 0.83) [51]. The rate of SAEs was higher (5% or greater) in patients treated with co-trimoxazole or doxycycline. This trial confirmed the previous EME-TIPAC data since a broader antibiotic therapy did not significantly improve clinical outcomes.

5.4. Analogues of prostacyclin

Treprostinil has gained approval in the USA for treating WHO group 1 pulmonary hypertension [52]. This analogue of prostacyclin may reduce the recruitment of fibrocytes, blocking fibrotic mechanisms and the production of ECM [53].

The INCREASE trial (NCT02630316) was a phase III RCT investigating efficacy and safety of treprostinil treatment in ILDs combinated with pulmonary hypertension. At week 16, the treatment group exhibited a significant positive impact in the 6-minute walk distance, with a least-squares mean difference of 31.12 m (95% CI, 16.85 to 45.39; $p < 0.001$) [54]. The subsequent post-hoc analysis, published in 2021, further revealed a significant enhancement in FVC in the treatment arm, particularly in patients with IPF [55]. These promising findings are currently undergoing validation in the prospective TETON study (ClinicalTrials.gov: NCT04708782). Representing the first program for an inhaled therapy in IPF, TETON comprises two 52-week double-blind phase 3 RCTs utilizing nebulizer solution treprostinil (Tyvaso) for IPF participants with or without pulmonary hypertension. The absence of an age restriction and inclusion of patients waiting for lung transplant add unique characteristic to the study. The primary endpoint has been identified in the change in absolute FVC over 52 weeks. This

novel route of administration could have additional benefits in terms of fewer AEs compared to oral and infusion drugs.

5.5. PDE4 inhibitors

PDE4 inhibitors, a drug class already approved for chronic obstructive pulmonary disease, primarily regulate inflammatory processes by selectively degrading cyclic adenosine monophosphate (cAMP), a second messenger crucial for physiological responses [56,57]. Among these, the oral drug BI 1,015,550 shows an inhibitory effect on phosphodiesterase 4B (PDE4B). The molecule seems to be able to attenuate bleomycin-induced pulmonary fibrotic processes in murine models through PDE4 inhibition [58]. This rationale is related to the pathophysiology of IPF, characterized by an inappropriate repair process involving inflammatory cells – neutrophils, monocytes, and T lymphocytes – along with elevated amounts of cytokines and growth factors, culminating in fibrotic lungs. Notably, PDE4 inhibitors exhibit distinct mechanisms, including suppression of macrophages release of profibrotic mediators, setting them apart from conventional anti-fibrotic agents [59,60].

BI 1,015,550 was investigated in a phase 2 RCT (ClinicalTrials.gov NCT04419506) [61]. Encompassing the period from August 2020 to October 2021, the research involved 147 participants, each receiving an oral dose of 18 mg twice daily, that limited a decline in pulmonary function over 12 weeks. The safety profile was generally acceptable, with gastrointestinal events being the most common AEs, involving 27% of the treatment group (compared to 16% with placebo). These promising findings will be further validated in the ongoing FIBRONEER trials, providing a comprehensive description of the safety profile as monotherapy or in combined therapy across a larger patient population. This comprehensive study encompasses two phase III RCTs, FIBRONEER-IPF (NCT05321069) for IPF participants and FIBRONEER-ILD (NCT05321082) for non-IPF progressive pulmonary fibrosis, both with and without approved antifibrotic therapies. The studies aim to evaluate the effectiveness and safety of the investigational drugs in treating patients with two different doses, either 9 mg or 18 mg twice daily, over a period of 52 weeks. The main endpoint includes the change (mL) in FVC from baseline to week 52, while secondary endpoints consists of rates of exacerbations, hospitalization due to pulmonary causes, or mortality.

5.6. FG-3019

FG-3019 (pamrevlumab) is a human monoclonal antibody that inhibits CTGF, a protein involved in biological processes related with abnormal tissue repair and tumorigenesis. Specifically, CTGF interacts with several regulators like VEGF, integrin receptor and TGF-β, regulating mechanisms of secretion, extracellular matrix synthesis, cell adhesion and motility [62].

In patients with IPF, efficacy and safety of pamrevlumab were investigated in a phase 2 PRAISE trial (NCT01890265) involving 103 participants [63]. Inclusion criteria included a radiological or histological diagnosis of IPF within 5 years, an age range of 40–80 years, mild-moderate functional deterioration, no concurrent standard antifibrotic therapy. The investigation drug was administered IV at a dosage of 30 mg/kg every three weeks for 48 weeks. Patients treated with FG-3019 had a statistically significant reduction in FVC decline compared to placebo and significant improvements in other functional measures such as DLCO [63]. The drug was well tolerated. The positive data of the PRAISE study have not been validated in the following phase 3 trials (ZEPHYRUS I & II). The primary endpoint was the absolute change in FVC at 48 weeks, while the secondary endpoint was the time to disease progression. Both endpoints were not satisfied in the ZEPHYRUS I trial, according to the results recently announced by FibroGen [64]. For this reason, despite of a good tolerability, ZEPHYRUS II was stopped.

5.7. Management of chronic cough

Interestingly, as there are no specific therapies for cough in IPF, a recent short term RCT investigated the role of oral nalbuphine (NAL), an opioid agonist – antagonist drug, in minimizing IPF-related cough [65]. These preliminary results demonstrated a rapid and marked reduction in cough. Following this, treatment with low dose controlled-release morphine was evaluated in a phase 2 RCT (PACIFY COUGH study; NCT04429516) that randomized 44 patients between 2020 and 2023. Patients were randomly assigned (1:1) to placebo twice daily or morphine 5 mg orally twice daily for two weeks followed by crossover after a 7-day washout period. A reduced objective cough counts over 14 days was observed with morphine treatment compared with placebo. The most common adverse events of morphine were nausea (14%) and constipation (21%) [66].

6. Efficiency of IPF trials

Pharmacological studies are facing numerous challenges aimed at gaining a greater comprehension of the various pathogenetic mechanisms of lung fibrosis, exploring potential combination treatments, managing comorbidities, and identifying genetic markers and prognostic methods. Designing RCTs versus placebo is hard, in cases of medical conditions of poor prognosis for which approved treatments exist (despite non-curative), as in the case of IPF. Studies involving patients affected by IPF should encompass patients already undergoing standard therapies. However, this may result in smaller margins for detecting significant efficacy differences, necessitating an increased number of participants and an extended study period [67]

A debate over finding the most reliable efficacy measure is currently ongoing. The traditional change in FVC over 12 months probably requires a time of enrollment disproportionately prolonged given the rapid deterioration observed in IPF. Other potential improvements may be the inclusion of outcomes like individual measures and the extension of lung fibrosis on chest TC. Moreover, every step of a novel pharmacological study should include examining subgroups based on biological differences or adopting a precision-based method.

Table 2. Recent and ongoing phase III RCTs investigating the efficacy and safety of novel IPF compounds.

Drug	Company/ Sponsor	Target	ClinicalTrials.gov ID	Program	Status	Primary endpoint	Start date	End date	Enrollment
BI 1,015,550	Boehringer Ingelheim	PDE4B	NCT05321069-NCT05321082	FIBRONEER-IPF and FIBRONEER-ILD	Recruiting	Absolute change from baseline in FVC at Week 52	September and October 2022, respectively	August and December 2024, respectively (estimated)	1117 and 1178, respectively (actual)
Inhaled Treprostinil	United Therapeutics Corporation	Fibroblast activity	NCT04708782	TETON	Recruiting	Absolute change from baseline in FVC at Week 52	June 2021	June 2025 (estimated)	576 (estimated)
Pamrevlumab (FG-3019)	FibroGen	CTGF	NCT03955146-NCT04419558	ZEPHYRUS I and II	Interrupted for futility	Change from baseline in FVC at Week 48	May 2019	June 2023	356 and 372, respectively
Ziritaxestat (GLPG-1690)	Galapagos NV	Autotaxin	NCT03711162-NCT03733444	GALAPAGOS ISABELA 1 and 2	Interrupted for futility	Annual rate of decline in FVC up to week 52	November 2018	March 2021	525 and 781, respectively
Recombinant human pentraxin-2 (rhPTX-2)	Hoffmann-La Roche	Innate immune response	NCT04552899-NCT04594707	STARSCAPE and STARSCAPE-OLE	Interrupted for futility	Absolute change from baseline in FVC at Week 52	March and August 2021, respectively	February 2023	665 and 117, respectively
Antimicrobials (co-trimoxazole or doxycycline)	Weill Medical College of Cornell University	Lung microbiome	NCT02759120	CleanUP-IPF	Interrupted for futility	Number of participants with first non-elective, respiratory hospitalization or all-cause mortality	March 2017	March 2020	513

Abbreviations: BI, Boehringer Ingelheim; CTGF, connective tissue growth factor; ID, identification; FG, FibroGen; FVC, forced vital capacity; GLPG, Galapagos; IPF, idiopathic pulmonary fibrosis; NCT, national clinical trial number; OLE, open-label extension; PDE4B, phosphodiesterase 4B; RCTs, randomized clinical trials.

Implementing such strategies may enhance the generalizability of RCT data.

7. Analyzing recent failures of phase III studies

Notable failures were encountered in recent phase III clinical trials (Table 2), necessitating careful consideration to deepen our understanding of IPF. Initial data of some drugs, promising in preclinical and phase 2 trials, have not been validated in greater and heterogenous study populations. Noteworthy among these failures are the premature termination of the GALAPAGOS ISABELA 1 and 2 studies in 2021 due to a higher rate of clinical deterioration and mortality in patients with IPF received ziritaxestat, the cessation of the STARSCAPE trial in November 2022 on recombinant human pentraxin-2 due to futility, and the discontinuation of clinical development in IPF of pamrevlumab in June 2023 following the failure of ZEPHYRUS I study.

8. Conclusion

IPF continues to pose as a serious respiratory condition despite significant strides have been achieved in comprehending and addressing IPF in recent years, along with improvements in trial efficiency. Prevalence of the disease steadily rising among individuals aged 65 and above. While the approved antifibrotics contribute to slowing down the extension of the fibrotic process, a notable proportion of patients face challenges in tolerating these interventions. As a result, ongoing research aims to explore new potent and well-tolerated therapeutic approaches, identifying drugs able to arrest or potentially restore the scarred lung tissue.

9. Expert opinion

There has been progress in pharmacological research in IPF with the goal of developing a definitive treatment capable of improving the course of the disease. Several clinical trials have been recently conducted to resolve the complexities of IPF, also representing a promising chance for many patients eager to participate. In fact, although treatments involving nintedanib and pirfenidone have gained widespread usage, they necessitate intricate clinical management within the vulnerable population of IPF patients. Moreover, they have a poor long-term tolerability and are unable to interrupt or reverse fibrotic processes.

Undoubtedly, the overarching objective is to optimize the clinical benefits and the tolerability of IPF treatments. This involves the anticipated validation of emerging targeted agents tailored to the individual characteristics of patients. Clinically, even preceding the starting of therapeutic interventions, crucial steps involve establishing an accurate diagnosis, as misdiagnosis may lead to inappropriate intervention.

Concurrently, efforts in pathophysiological studies, particularly focusing on biological processes that drive and sustain pulmonary fibrosis, are essential. The evaluation of these processes in both animal models and biological samples from patients [3,68] holds significant promise for advancing our understanding of IPF. Different drugs are currently evaluated

in phase II studies, exhibiting multiple effects targeting specific processes, with different methods of administration. Oral drugs have a more comfortable administration for IPF fragile patients, compared to molecules with IV administration that need several healthcare resources. Interestingly, the potential inhalation route of some molecules under investigation, such as inhaled treprostinil, could reduce the rate of systemic AEs.

Preclinical studies in IPF have demonstrated promising therapeutic data. For example, sumatriptan, a selective 5-$HT_{1B/1D}$ receptor agonist, has shown potential in modulating α-SMA and inflammation. Additionally, saracatinib, a selective Src kinase inhibitor, may have an inhibitory effect on fibrogenic responses [69], while the aerosolized thyroid hormone (TH) can increase survival and resolve fibrosis in mouse models of pulmonary fibrosis [70]. Moreover, the programmed cell death-1 (PD-1) inhibitor pembrolizumab may exert antifibrotic effects, supported by data indicating consistent increases in PD-1 levels in mediastinal lymph nodes of IPF patients and in tracheobronchial lymph nodes of bleomycin-treated mice [71].

The generalizability of the eligibility criteria commonly adopted in RCTs on IPF may be limited, as they often do not account for personal discrepancies within single patients enrolled in the clinical trials. The PRAISE study, for example, revealed a sex disparity among participants other than an elevated dropout rate, mostly among individuals with worst cases of IPF. Furthermore, the FLORA trial faced some challenges, including a limited number of randomized patients and a relatively brief expected study period. The well-designed ISABELA phase studies faced early termination due to the COVID-19 pandemic, resulting in an inability to achieve the expected sample size and incomplete data collection. Finally, in phase III RCTs on pamrevlumab and zinpentraxin, the planned treatment period could be excessively prolonged given the typical rapid clinical deterioration of IPF.

While the change in FVC is traditionally considered the main efficacy measure, integrating clinical data like mortality or the rate of pulmonary-related hospital admissions may offer a more complete approach. Enrolling participants affected by different severities of IPF would also align better with real-world clinical practice.

Additional research is required to explore the potential synergistic benefits that may arise when novel agents are added to the existing approved therapies. Identifying increasingly specific targets and consistently refining the study methodology also represent crucial goals. This multifaceted approach is anticipated to significantly enhance the overall management of IPF patients, supporting the optimistic expectations of reversing fibrotic alterations and ultimately restoring lung function to a normal state.

Abbreviations

6MWD 6-minute walk distance;
AEs adverse events;
ALAT Latin American Thoracic Association;
ATS American Thoracic Society;
ATII alveolar type II;
ATX autotaxin;
cAMP cyclic adenosine monophosphate;
CI confidence interval;
CTGF connective tissue growth factor;
CYP3A4 Cytochrome P450 3A4;
DLCO diffusing capacity of the lung for carbon monoxide;
ECM extracellular matrix;
EMA European Medicines Agency;
ERS European Respiratory Society;
FDA Food and Drug Administration;
FGF-2 fibroblast growth factor 2;
FGFR fibroblast growth factor receptor;
FVC forced vital capacity;
HR hazard ratio;
HRCT high resolution computed tomography;
IGF-1 insulin-like growth factor 1;
IL interleukin;
ILD interstitial lung disease;
IPF idiopathic pulmonary fibrosis;
IV intravenous;
JRS Japanese Respiratory Society;
LPA lysophosphatidic acid;
mL millilitre;
MUC5B mucin 5B;
NAL nalbuphine;
NCT national clinical trial number;
OLE open-label extension;
PD-1 programmed cell death-1;
PDE4B phosphodiesterase 4B;
PDGF platelet-derived growth factor;
PF-ILD progressive fibrosing interstitial lung disease;
PFD pirfenidone;
RCTs randomized clinical trials;
rhPTX-2 recombinant human pentraxin-2;
RNA ribonucleic acid;
RTK receptor tyrosine kinase;
SAE serious adverse event;
TERC telomerase RNA component;
TGF transforming growth factor;
TH aerosolized thyroid hormone;
UIP usual interstitial pneumonia;
VEGFR vascular endothelial growth factor receptor.

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