Review

OPEN ACCESS

Pharmacological treatment in Idiopathic Pulmonary Fibrosis: current issues and future perspectives

Enrico Sciacca[1,§], Giuseppe Muscato[1,§], Lucia Spicuzza[1], Mary Fruciano[1], Elisa Gili[1], Gianluca Sambataro[2,3], Stefano Palmucci[4], Carlo Vancheri[1,‡], Alessandro Libra[1,‡]

[1]Department of Clinical and Experimental Medicine, "Regional Referral Center for Rare Lung Diseases", University - Hospital Policlinico "G. Rodolico- San Marco", University of Catania, Catania, Italy; [2]Artroreuma s.r.l., Rheumatology outpatient Clinic, Mascalucia (CT), Italy; [3]Internal Medicine Unit, Department of Clinical and Experimental Medicine, Division of Rheumatology, Cannizzaro Hospital, University of Catania, Catania, Italy; [4]Department of Medical Surgical Sciences and Advanced Technologies "GF Ingrassia", University -Hospital Policlinico "G. Rodolico-San Marco", Unità Operativa Semplice Dipartimentale di Imaging Polmonare e Tecniche Radiologiche Avanzate (UOSD IPTRA), Catania, Italy. [§]These authors contributed equally to this work and share the first authorship; [‡]These authors contributed equally to this work and share the last authorship. This manuscript is part of the activities belonging to the ERN-LUNG project.

ABSTRACT

Abstract: Idiopathic pulmonary fibrosis (IPF) represents a fibrotic interstitial lung disease characterized by uncertain etiology and poor prognosis. Over the years, the path to effective treatments has been marked by a series of advances and setbacks. The introduction of approved antifibrotic drugs, pirfenidone and nintedanib, marked a pivotal moment in the management of IPF. However, despite these advances, these drugs are not curative, although they can slow the natural progression of the disease. The history of drug therapy for IPF goes together with the increased understanding of the pathogenic mechanisms underlying the disease. Based on that, current research efforts continue to explore new therapies, possible personalized treatment strategies, drug combinations, and potential biomarkers for diagnosis and prognosis. In this review, we outline the route that led to the discover of the first effective therapies, ongoing clinical trials, and future directions in the search for more effective treatments.

Key words: idiopathic pulmonary fibrosis, IPF, treatment, therapy, future perspectives

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a fibrotic interstitial lung disease of uncertain origin, exhibiting radiological and histological characteristics consistent with usual interstitial pneumonia (UIP)[1]. It is a rare condition with an estimated global prevalence of about 4 cases per 10,000 persons [2], with a poor prognosis considering a median survival of 3-5 years since diagnosis [3].

IPF predominantly impacts the elderly population, affecting lungs insidiously and revealing itself through exertional breathlessness and a non-productive cough. As the disease advances, individuals may encounter a reduction in exercise capacity, eventually culminating in respiratory failure. IPF should be considered in adult patients with unexplained, persistent exertional breathlessness, cough, bibasilar inspiratory crackles, without constitutional or other symptoms indicative of a multisystem disorder [1].

Correspondence: Prof. Carlo Vancheri, Department of Clinical and Experimental Medicine, "Regional Referral Center for Rare Lung Diseases", University - Hospital Policlinico "G. Rodolico- San Marco", University of Catania, Catania, Italy, E-mail: vancheri@unict.it

Authors' contributions: ES and GM contributed equally to this work and share the first authorship; CV and AL contributed equally to this work and share the last authorship. All authors approved the final version and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate: Not applicable.

Data availability statement: Available from the Corresponding author on reasonable request.

Conflict of interest: The Authors declare no conflict of interest.

Funding: None.

The clinical trajectory is further complicated by concurrent conditions such as pulmonary hypertension and emphysema, leading to heightened morbidity and mortality [3–6]. Accurate and timely diagnosis of IPF is crucial for implementing appropriate management strategies. High-resolution computed tomography (HRCT) scans and lung biopsy remain integral to the diagnostic process, and the recent guidelines provide a structured approach for their administration [1,7].

Over the years, the management of IPF has undergone significant developments, especially in the realm of pharmacological therapy aimed at slowing the disease progression and trying to improve patients' quality of life. The history of pharmacological therapy in IPF has witnessed significant advancements over the years, increasing the focus on understanding the underlying pathogenetic mechanisms responsible for disease progression, with the goal of developing novel targeted therapies. The introduction of the U.S. Food and Drug Administration and European Medicines Agency-approved antifibrotic drugs pirfenidone and nintedanib has marked a turning point in IPF management. Pirfenidone, a collagen synthesis inhibitor, has undergone thorough clinical investigations, including the CAPACITY study, demonstrating its ability to slow disease progression and improve patient survival [8,9]. Similarly, nintedanib, a multikinase inhibitor, has shown efficacy in reducing lung function decline in studies such as INPULSIS [10]. These molecules, through their antifibrotic action, have provided a solid foundation for current therapeutic guidelines[1,7]. Despite these advances, pirfenidone and nintedanib are not able to reverse or resolve pre-existing fibrosis. Thus, patients continue to experience lung function deterioration while on treatment, which remains focused on slowing progression of fibrosis, maintaining comfort and, in late stages, on palliative care.

To find a cure for this debilitating and fatal disease, it is imperative to deepen our understanding of the pathogenetic mechanisms underlying IPF, including altered cell-cell crosstalk and secretion of pathogenic molecules in the fibrotic milieu. Ongoing research continues to explore novel therapeutic options, personalized strategies and therapeutic combinations as well as possible biomarkers of diagnosis and/or predictors of treatment efficacy [11]. In this review, we provide a comprehensive summary of the current pharmacological treatments of IPF, clinical trials and future directions.

Pathogenesis and molecular pathways involved in lung fibrosis

IPF is characterized by the accumulation of collagen-producing fibroblasts and myofibroblasts, resulting in aberrant production and deposition of extracellular matrix, including collagens and fibronectin, leading to a progressive and irreversible fibrogenic process and loss of organ function [12]. Although several risk factors, including cigarette smoke, air pollution, and aging, are known to be involved in the development of IPF, the causes of IPF remain unknown[13–15]. Currently, the most accredited hypothesis is that, in genetically predisposed individuals, recurrent alveolar epithelial cells damage may lead to an increased release of cytokines and chemokines by alveolar epithelial cells and recruitment of cells responsible for perpetuating damage and incessant production of extracellular matrix [16]. This mechanism determines an increased secretion of fibrogenic signaling molecules, such as transforming growth factor-β (TGF-β) by activated macrophages that promote recruitment, proliferation and differentiation of fibroblast into myofibroblasts (Figure 1) and alter the balance between collagen synthesis and collagen degradation[17,18]. Moreover, TGF-β acts as an inducer for other fibrogenic molecules secretion such as connective tissue growth factor (CTGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF). In addition, telomerase gene mutation, short telomeres, aging, and cellular senescence play a role in the pathogenesis of IPF decreasing the population of type II alveolar epithelial cells and reducing their role in tissue injury repair[19].

IPF treatment in the past: more shadows than lights

The inflammatory model

From its initial characterization, the treatment of IPF has traditionally relied on the assumption that

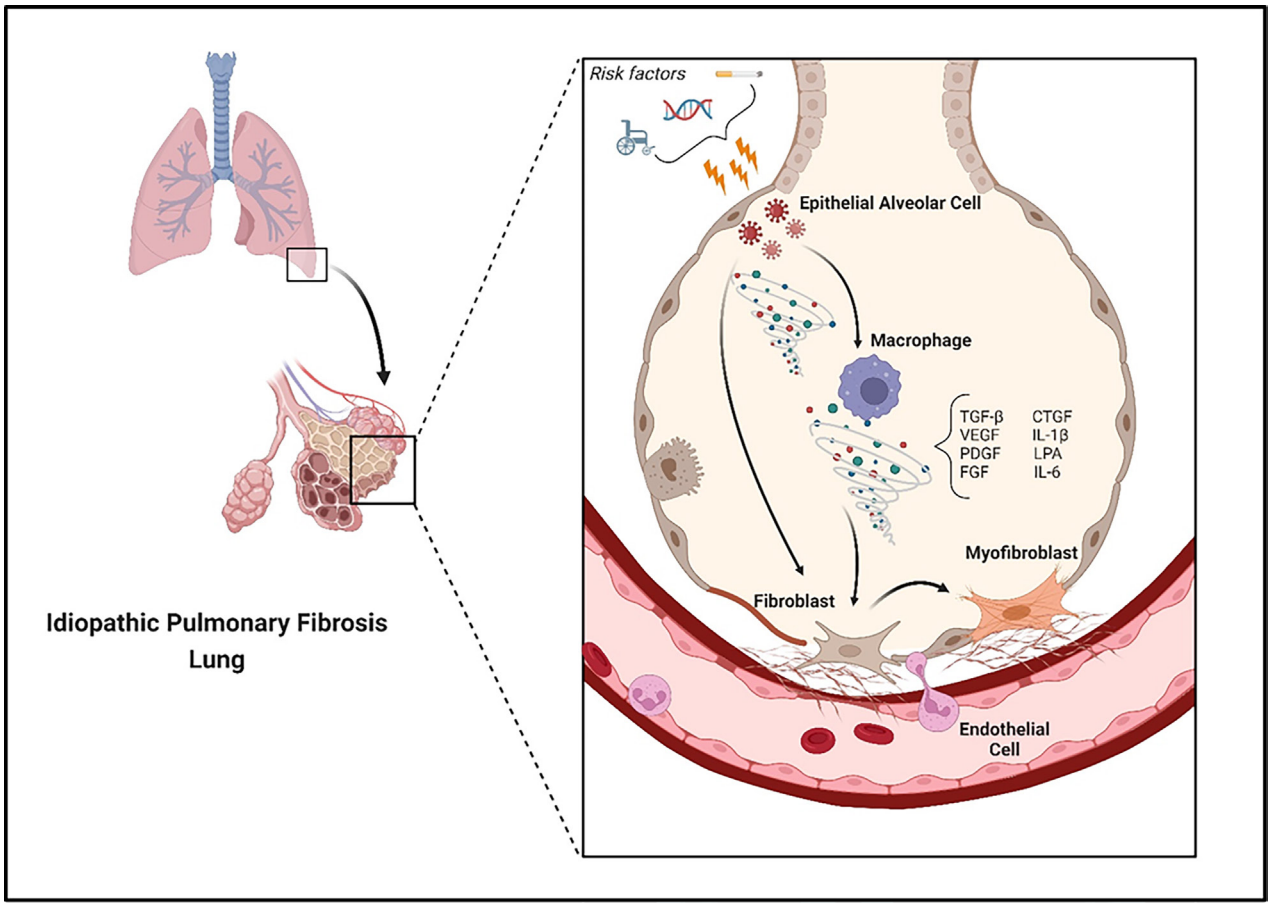

Figure 1. Cell types and cytokines involved in the pathogenesis of IPF. Lung fibrosis is the result of different pathways, assuming a possible trigger related by risk factors (as aging, smoking or genetic mutations) and the uncontrolled secretion of cytokines by epithelial alveolar cells, macrophages and endothelial cells responsible for the activation of fibroblasts and their transition to myofibroblasts. Legend: TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; FGF: fibroblast growth factor; CTGF: connective tissue growth factor; IL-1β, Interleukyn-1β, LPA, lysophosphatidic acid; IL-6, Interleukyn-6. Created with Biorender.com; all rights reserved.

injury leads to inflammation and fibrosis [20]. Consequently, corticosteroids have been the mainstay of IPF treatment for several years, even because no pharmacological therapy has been proven to alter or reverse the inflammatory process of IPF.

Until 1999, treatment options included corticosteroids, immunosuppressive/cytotoxic agents (e.g., azathioprine, cyclophosphamide), and antifibrotic agents (e.g., colchicine or d-penicillamine) either alone or in combination [21–27].

In 2000, for the first time an International Statement Consensus recommended a combined therapy involving corticosteroid and either azathioprine or cyclophosphamide. However, it acknowledged the high risk of treatment failure due to insufficient data from randomized clinical trials (RCTs)[28].

Supporting the inflammatory pathogenesis hypothesis, the IFIGENIA study, a multicenter, randomized, double-blind, placebo-controlled investigation, assessed outcomes in individuals receiving either N-acetylcysteine (NAC) or a placebo plus prednisone and azathioprine. The trial revealed a diminished rate of decline in Forced Vital Capacity (FVC) and Diffusing Capacity of the Lungs for Carbon Monoxide (DL_{CO}) among patients treated with NAC, although no improvement in one-year survival was observed [29].

A more definitive response regarding steroids and immunomodulating agents came by PANTHER-IPF, a multicenter randomized controlled trial to assess the efficacy of prednisone, azathioprine, and NAC. In the PANTHER-IPF trial, patients with IPF and mild-to-moderate lung function impairment, underwent randomization into three groups: prednisone, azathioprine, and NAC (combination therapy); NAC alone; or placebo. Combination therapy with prednisone, azathioprine and NAC, compared with placebo, was associated with increased all-cause mortality, all-cause hospitalizations and treatment-related severe adverse events. It was observed that elevated mortality and hospitalization rates manifested early in the trial, closely aligning with the period of escalated prednisone dosage, tapered over the initial 4-6 months to a minimal daily dose[30]. This observation implies that the heightened toxicity seemed to be attributed to high-dose corticosteroids rather than the azathioprine and low-dose prednisone.

Role of interferon gamma as a potential inhibitor of profibrotic cytokines

The imbalance between pro-fibrotic and anti-fibrotic cytokines in the pathogenesis of IPF prompted the exploration of interferon gamma (IFN-γ) in clinical trials. IFN-γ has exhibited the capacity to inhibit fibroblast proliferation and reduce the expression of TGF-β, PDGF, and various other pro-fibrotic interleukins in both *in vitro* and *in vivo* investigations [31]. After an encouraging preliminary study limited by a small number of patients enrolled [32], a placebo-controlled trial demonstrated that interferon gamma-1b did not affect progression-free survival or pulmonary function [33]. However, the larger prospective INSPIRE study did not demonstrate any survival advantage with subcutaneous IFN-γ treatment [34].

A change of target: endothelin system and phosphodiesterase-5 inhibitor

Several studies had demonstrated the profibrotic role of endothelin-1, molecule secreted by fibroblasts, endothelial cells, alveolar macrophages, epithelial cells and polymorphonuclear leukocytes, and able to increase collagen production and reduce synthesis of interstitial collagenase [35–38]. Based on these premises, the BUILD-1 trial sought to prove the efficacy of bosentan, a dual endothelin receptor antagonist (ERA), on exercise capacity and time to disease progression in patients with IPF[39]. Treatment with bosentan in IPF patients did not show superiority over placebo in the primary endpoint of change from baseline to month 12 in the 6-minute walk test (6MWT) distance. However, a trend favoring bosentan was observed in the secondary endpoint related to time to IPF worsening or death [39]. This endpoint was re-evaluated in another clinical trial (BUILD-3) with a larger number of patients, where drug tolerability was demonstrated, but the primary objective was not achieved [40].

Among endothelin receptor antagonists, ambrisentan, an ETA receptor-selective antagonist, was also assessed in a clinical trial to evaluate its efficacy in reducing the progression rate of IPF patients. In this trial, ARTEMIS-1, ambrisentan was terminated early due to a lack of efficacy in treating IPF and an increased risk of disease progression and respiratory hospitalizations [41].

The MUSIC trial was a phase II randomized controlled trial aimed at examining the effectiveness and safety of dual endothelin receptor antagonist, macitentan (10 mg once daily) on forced vital capacity (FVC), in individuals with histologically confirmed IPF compared to placebo. Although the promising preliminary data, the primary objective of the MUSIC trial was not achieved as no notable difference between treatments was observed in the primary outcome of changes from baseline up to month 12 in FVC [42].

Another therapeutical option explored has been sildenafil, a phosphodiesterase-5 inhibitor whose mechanism of action stabilizes the second messenger of nitric oxide, cyclic guanosine monophosphate, which leads to pulmonary vasodilatation [43]. It was evaluated in an RCT, based on the hypothesis that it might improve blood flow to well-ventilated regions of the lung, improving ventilation/perfusion ratio, in patients with advanced idiopathic pulmonary fibrosis. The study, including 180 patients, did not show benefits for patients underwent treatment with sildenafil,

not reaching the primary endpoint settled as increase in 6MWT distance [44].

Current approved therapies

With an evolving understanding of the role of fibroblasts and TGF-β, the search for a truly effective drug for pulmonary fibrosis, going beyond the purely inflammatory hypothesis considered up to then, has focused on the anti-fibrotic role of the molecules under study. The first antifibrotic molecule studied was pirfenidone, tested in murine models of bleomycin-induced fibrosis [45] and then its activity had been confirmed in human cells [45]. Pirfenidone demonstrated effective inhibition of fibronectin and the synthesis of α-smooth muscle actin (α-SMA), a critical factor in the fibroblast-to-myofibroblast transition, as induced by TGF-β in human lung fibroblasts. Furthermore, pirfenidone exhibited suppressive effects on fibrotic alterations mediated by TGF-β in human fetal lung fibroblasts [46,47]. In 1999, the first open-label study evaluating efficacy and safety of pirfenidone for IPF patients, showed the capacity to arrest the further decline of lung function in most patients with acceptable tolerability and minimal side effects [48]. Another encouraging result derives from a second open-label study in patients with advanced IPF with effects on stabilization of disease, but survival was not prolonged, probably due to the short treatment duration of 1 year [49]. Subsequent studies confirmed efficacy of pirfenidone, demonstrating an increased progression-free survival time and slowing down vital capacity (VC) deterioration [50,51]

Two Phase III international randomized double-blind placebo trials (CAPACITY 004 and CAPACITY 006) tried to evaluate change in percent predicted forced vital capacity (ppFVC) [52]. The CAPACITY 004 study included 435 patients treated with high-dose pirfenidone (2,403 mg/day), low-dose pirfenidone (1,197 mg/day) or placebo, while the CAPACITY 006 study included 344 patients treated with exclusively high-dose pirfenidone or placebo. While the CAPACITY 004 trial demonstrated a significant difference in FVC% and progression-free survival from baseline over 72 weeks between high-dose pirfenidone and the placebo arm, the CAPACITY 006 trial showed a difference in the reduction in FVC% rate of decline up to week 48 in the pirfenidone group, with no difference at week 72, thus failing the primary endpoint.

Subsequently another randomized, double-blind, placebo-controlled Phase III trial was conducted in 2014 to support the approval of pirfenidone for IPF therapy. In ASCEND trial, treatment with pirfenidone resulted in a significant between-group difference in the change from baseline to week 52 in the percentage of the predicted FVC versus placebo. Patients treated with pirfenidone also recorded a significant reduction in decline of the 6MWT distance and a longer progression-free survival, with gastrointestinal and skin-related side effects rarely causing discontinuation [53].

Further analysis of population of CAPACITY and ASCEND trials proved that pirfenidone significantly reduced the relative risk of all-cause mortality at 1 year by 48% and the risk of IPF-related mortality at 1 year by 68% [54].

Finally, real-world data has shown overall efficacy and tolerability of pirfenidone on reducing FVC decline in patients with IPF [55–57].

Riding the hypothesis of the role of TGF- β in lung fibrogenesis, scientific research evaluated the role of tyrosine kinase inhibitors as a possible therapeutic option. Protein kinases have been associated with the fibrogenic process mediated by growth factors like TGF-β [58]. In the management of IPF, tyrosine kinase inhibitors (TKIs) have been employed to selectively inhibit the function of fibroblasts, pivotal effector cells in the progression of IPF. Imatinib mesylate is a TKI with activity against the platelet-derived growth factor receptors (PDGFR-α and -β), discoidin domain receptors (DDR1 and DDR2), c-kit, and c-Abl [59]. A randomized, placebo-controlled trial evaluated safety and clinical effects of imatinib in patients with mild to moderate IPF followed for 96 weeks, but among all patients, 29% discontinued the study causing the failure to achieve the primary endpoint. The results of this trial showed that imatinib did not affect either survival or lung function [60].

On the other hand, the beginning of cellular signaling cascades via tyrosine kinases like vascular endothelial growth factor (VEGF), FGF and PDGF

has been implicated in pathogenesis of IPF [61]. Nintedanib is an intracellular antagonist that selectively targets a spectrum of tyrosine kinases, including the receptors for VEGF, FGF, and PDGF [62,63].

Based on these fundamental concepts, it was suggested that nintedanib could have a role in slowing FVC decline in patients with IPF. In TOMORROW trial, a phase II trial, four oral doses of nintedanib were compared to placebo in patients with IPF, demonstrating that a dose of 150 mg twice daily of nintedanib, compared with placebo, was associated with a slower loss of lung function (benefit of 68.4%, p = 0.06). The same dosage also led to a markedly reduced occurrence of acute exacerbations (p = 0.02) and enhanced quality of life (as assessed by the St. George's Respiratory questionnaire) compared to the placebo (p = 0.007) [64]. Those encouraging data stimulate the investigation of phase III trials, in INPULSIS-1 and INPULSIS-2 trial, that were both one year-long randomized, placebo-controlled trials examining the efficacy of 150 mg twice daily, using as primary endpoint the annual rate of decline in FVC [10]. In both trials nintedanib significantly reduced the rate of FVC decline, with the adjusted annual change in the nintedanib group that was -114.7 mL compared to -239.9 mL in the placebo group (p < 0.001) in INPULSIS-1, and -113.6 mL in the nintedanib group versus -207.3 mL in the placebo group in INPULSIS-2. The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups in INPULSIS-1, and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2. Adverse events led to discontinuation in less than 5% of patients [10].

Although nintedanib and pirfenidone showed a reduced rate of diseases progression in patient with IPF, those therapies remain an option for increases survival but they are not curative; in fact the disease was still progressive and led to death for respiratory failure. In 2018, with the availability of two antifibrotic drugs recommended for the treatment of IPF, an approach based on a combination therapy was proposed. The hypothesis was that an add-on therapy might provide a synergic effect with more benefit compared to monotherapy with one only antifibrotic drug. The INJOURNEY trial aimed to evaluate safety and tolerability in patient treated with nintedanib and add-on pirfenidone (titrated to 801 mg three times daily) versus nintedanib alone, enrolling patients who completed 4- to 5-weed run-in with nintedanib 150 twice daily who were not required reduction or interruption of treatment during the run-in period [65]. Main results of the trial were that gastrointestinal adverse events were reported in 69.8% of patients treated with nintedanib with add-on pirfenidone and 52.9% treated with nintedanib alone. Exploratory efficacy evaluation demonstrated at week 12 changes from baseline in FVC of -13,2 ml and -40.9 ml in patients treated with nintedanib with add on pirfenidone and nintedanib alone. Despite add-on therapy showed a manageable safety and tolerability profile in patients with IPF and exploratory analysis proved a possible efficacy on FVC decline, no further larger controlled studies has been performed to confirm the benefit/risk ratio of combination therapy.

Last findings and the importance of learning from what went wrong

The introduction of the aforementioned drugs has represented a milestone and a revolution on the history of IPF treatment, although it might be considered only the tip of the iceberg considering the increasing interest and research efforts made by the scientific community since the begin of the third millennium. In fact, according to ClinicalTrial.gov [66], the largest database of clinical research studies supported by the National Institute of Health, only in the last 10 years there have been registered more than 100 phase II and phase III interventional clinical trials evaluating safety and/or efficacy of different treatments in IPF patients, including brand new molecules or already known ones with a possible acting role in the pathophysiology of the disease.

Despite these numbers and although several molecules have shown a promising profile and encouraging results, pirfenidone and nintedanib remain so far, the only two drugs with proven efficacy in IPF [67].

Better understanding of the mechanism behind the development of fibrosis allowed the proposal of drugs with a variety of different targets. The role of the Lysophosphatidic acid (LPA) is one of the most recently studied theme in the onset of lung fibrosis[68].

LPA is a phospholipid mediator able to activate a growth factor-like response in pulmonary fibroblasts, smooth muscle cells and epithelial cells, all expressing a specific receptor, $LPAR_1$[69,70]. It has been demonstrated that both in animal model of lung fibrosis (Bleomycin induced) and in IPF patients' tissue and bronchoalveolar lavage (BAL), LPA have increased concentrations compared to healthy controls [69]. The enzyme responsible for production of LPA is Autotaxin (ATX), a secreted glycoproteic Lysphospholipase D mainly expressed by alveolar epithelial cells, macrophages and weakly in fibroblasts too [71]. As seen for LPA, ATX levels in BAL and lung tissue are higher in IPF than in healthy controls [68], so it has been proposed as potential therapeutical target in IPF with the introduction of its selective inhibitor zirtaxestat. This molecule showed promising efficacy results in the FLORA study, a phase 2a randomized placebo-controlled trial, despite the fact that it was designed to evaluate the safety of zirtaxestat in patients either under standard of care treatment or drug-free [72]. The evaluation of zirtaxestat efficacy in IPF patients was the aim of the ISABELA I and ISABELA II trials, two identically designed phase 3 randomized clinical trials, whose results have been recently published[73]. Unfortunately, both studies have been interrupted early after an interim analysis revealed an increased mortality in the patient group receiving a 600 mg daily dose and a lack of efficacy in all the treatment groups. In fact, ziritaxestat did not improve the annual rate of decline for FVC vs placebo: in the ISABELA 1 trial, the mean rate of decline for FVC at week 52 was −124.6mL (95% CI, −178.0 to −71.2 mL) with 600 mg, −173.9 mL (95% CI, −225.7 to −122.2 mL) with 200 mg, and −147.3mL (95%CI, −199.8 to −94.7 mL) with placebo. In the ISABELA 2 trial, the mean annual rate of FVC decline at week 52 was −173.8 mL (95% CI, −209.2 to −138.4 mL) with 600 mg, −174.9 mL (95% CI, −209.5 to −140.2 mL) with 200 mg, and −176.6 mL (95% CI, −211.4 to −141.8 mL) with placebo [73]. Moreover, pooled data showed all-cause mortality was 8.9% with 600mg and 7.0% with 200mg vs 5.5% with placebo (HR 1.8 [95%CI,1.1 to 3.0] for 600mg of ziritaxestat vs placebo and HR 1.3 [95%CI, 0.8 to 2.3] for 200mg ziritaxestat vs placebo). Furthermore, all secondary outcomes were unmet.

The discrepancy of these findings with what obtained in the FLORA study may be explained by the strong limitations of the phase 2a trial, represented by the small sample size and the short duration. The ISABELA I and ISABELA II trials enrolled 1,306 individuals affected by IPF and the design of the studies has been not considered as a factor leading to these findings [73], but they highlighted the importance of basing phase 3 trial on high-quality preclinical and clinical data, adaptive designs with a Bayesian approach and using biomarker-based enrichment strategies with prognostic biomarkers [73,74].

The ATX/LPA axis is still object of other studies, specifically a phase II RCT on the efficacy and safety of BMS-986278, an antagonist of $LPAR_1$ [74], that has recently completed the recruitment phase (NCT04308681). This study was designed for two cohorts, an IPF cohort and a progressive fibrosing interstitial lung diseases (PF-ILD) cohort[75]. The IPF cohort included three different groups based on daily drug dosage (60mg, 30mg and placebo) with 278 patients randomized and 276 receiving treatment [76]. The primary endpoint was rate of change in percent predicted FVC from baseline through 26 weeks as assessed based on two prespecified estimands [76]: the treatment policy estimand (similar to an Intention-to-Treat [ITT] analysis) included all observed data regardless of dose reduction and provides an estimate of efficacy with dose reduction as part of the treatment regimen; and the while-on-treatment estimand included all observed data prior to dose reduction and provides an estimate of efficacy without dose reduction as part of the treatment regimen. Treatment with 60 mg of BMS-986278 led to a 62% relative reduction in the rate of change in ppFVC versus placebo in the while-on-treatment analysis, and a 54% reduction versus placebo in the treatment policy analysis. A prespecified Bayesian analysis was utilized to provide the probability of a positive treatment difference for BMS-986278 compared to placebo: it showed a greater than 95% probability that 60 mg of BMS-986278 was superior compared to placebo in reducing the rate of decline in ppFVC over 26 weeks in both the while-on-treatment and treatment policy estimands. Subgroup analyses demonstrated a treatment effect of 60-mg BMS-986278 with or without

background antifibrotics. The 30 mg dose was not effective compared to placebo [76]. BMS-986278 was well tolerated in both treatment arms with rates of adverse events, including rates of gastrointestinal side effects, and treatment discontinuation comparable to placebo. These findings represented the basis for the design and initiation of the ongoing phase 3 clinical trial evaluating the effectiveness of BMS-986278 in IPF (NCT06003426).

The study of new and specific targets in the pathways leading to lung fibrosis has allowed the proposal of the use of monoclonal antibodies (MABs) in IPF too, considered as potential tailored therapy with a low rate of adverse events related to their assumption, as shown in other conditions like severe asthma, connective tissue diseases and some forms of cancer [77,78]. Several MABs have been evaluated as candidate treatments for IPF [77], but the only one that has reached and terminated a phase III RCT is pamrevlumab, a fully human recombinant monoclonal antibody against connective tissue growth factor (CTGF), a cytokine produced by fibroblasts, myofibroblasts, and endothelial cells [79]. CTGF is thought to interact with various regulatory modulators, such as TGF-β, vascular endothelial growth factor (VEGF), and receptors such as integrins modulating cellular responses that are associated with aberrant tissue repair and tumorigenesis[80]. The PRAISE study, a phase II RCT, showed that 30mg/kg of pamrevlumab intravenously administered every 3 weeks significantly attenuated the decline in lung function compared with placebo [80], resulting in a mean change in percentage of predicted FVC from baseline to week 48 was −2,9% in the pamrevlumab group compared with −7,2% in the placebo group (between-group difference 4.3% [95% CI 0.4–8.3]; p=0.033), which corresponded to a relative reduction in percentage of predicted FVC decline of 60.3% in patients treated with pamrevlumab. An interesting secondary outcome proposed and met in this trial concerned the imaging with a quantitative score for the lung fibrosis in HRCT (expressed in volume of the classified voxels of lung fibrosis or interstitial lung disease with respect to a segmented whole lung) which resulted significantly lower in the pamrevlumab group than in the placebo group at week 24 (24.8 mL vs 86.4 mL; p=0.009) and this difference was maintained to week 48 (75.4 mL vs 151.5 mL; p=0.038). Due to these findings, the phase III trials Zephyrus I and Zephyrus II (NCT03955146, NCT04419558) were launched to confirm the effectiveness of this drug. In these trials, pamrevlumab treatment did not meet the primary endpoint of change from baseline in forced vital capacity (FVC) at week 48, with a mean decline in FVC from baseline to week 48 of 260 ml in the pamrevlumab group compared to 330 ml in the placebo arm (p=0.29). And, although safety analysis confirmed pamrevlumab was generally safe and well tolerated and the majority of treatment emergent adverse events were mild or moderate, the secondary endpoint considering the disease progression (FVC percent predicted decline of ≥10% or death) was also not met [81].

Another example of a promising molecule whose efficacy has been investigated in a phase III RCT, which unfortunately was discontinued early, is the Recombinant Human Pentraxin-2 (PRM 151). Pentraxin 2, also known as purified serum amyloid P, is a circulating endogenous regulator of tissue repair, able to inhibit the differentiation of monocytes into profibrotic macrophages and fibrocytes, also decreasing the production of TGF- β[82]. It has been demonstrated that serum levels of pentraxin 2 are significantly lower in individuals affected by IPF compared with healthy controls [83]. A phase II trial in which PRM 151 was administered intravenously every 3 weeks, had showed promising results, meeting the primary efficacy end point consisting in a significant difference between the least-squares mean change in percent predicted FVC value from baseline to week 28 in the treatment group compared with the placebo (−2,5% vs −4,8% of the placebo group, difference of -2.3% - 90%CI, 1.1 to 3.5; P= 0.001), and obtaining a positive result considering the Least-Squares mean change in 6-Minutes Walk distance from baseline to week 28 (−0,5 m in the treatment group vs −31.8 m in the placebo arm, with a difference of 31.3 m - 90% CI, 17.4 to 45.1; P < .001) [84]; due to these data the phase III study STARSCAPE (NCT04552899) was subsequently started. In spite of these encouraging findings, in February 2023 the Sponsor decided to interrupt the phase III trial after a futility analysis indicating that the study was unlikely to meet the predefined primary objective of the study.

The reason for this might not have a univocal explanation: while admittedly it could be true that some of the analysed molecules are ineffective in treating IPF, the reverse may still be true; we must still improve on phase II trials to yield more robust and reliable data, which will allow us to design high quality phase III studies. As stated by Podolanczuk et al., the crucial points for avoiding current issues in future clinical trials are several [85]: phase II trials must be sufficiently powered to assess safety and heterogeneity of treatment response considering background antifibrotic use, underlining so the importance of an adequate sample size, considering then ethnic and sex differences, with the option to use reliable biomarkers in future for a precision-based approach. Another point to evaluate is to consider other outcomes: longitudinal change of FVC is recognized as the most clinically relevant parameter in IPF, due to its demonstrated correlation to death; but sometimes its measurement might be susceptible to missing data or patient difficulties in performing spirometry. For this reason, adding other outcome such as death for any causes and hospitalization for worsening of the respiratory condition could be considered in the future, as showed in the CleanUP-IPF, a trial demonstrating the inefficacy of the addition of co-trimoxazole or doxycycline to standard of care for the treatment of IPF [86]. This crucial point in the future of clinical trials in IPF has been the theme of a recent symposium lead by some of the maximum experts of the field, including also regulatory representatives and patients advocates which evaluating the role of functional measurements (FVC, 6MWT), patient reported outcomes (PROs), imaging markers and circulating biomarkers, expressed the need to go beyond FVC as the only primary outcome in RCT [87], underlining the importance of composite outcome and proposing the integration of adequately validated PROs as key-endpoints in the future, making a better understanding of patients feels and function.

Promising molecules in ongoing clinical trials

There are numerous ongoing clinical trials considering the different targetable pathways in idiopathic pulmonary fibrosis. It is important to note that molecules and trials mentioned in this review which have not completed phase 3, are not assessed based on a definitive evaluation of data, but are only considered for their potential, based on the current state of shared information. Table 1 shows the most recent and current phase 3 randomized clinical trials on IPF.

The anti-inflammatory and immunomodulatory function of PDE4 is already documented in literature, leading to its use in COPD and psoriasis/psoriatic arthritis with roflumilast and apremilast, respectively [88,89]. A third PDE4 inhibitor, crisaborole, was approved for topical treatment of mild-to-moderate atopic dermatitis [90]. None of these show any preferential enzymatic inhibition among the four PDE4 subtypes, A–D. Phosphodiesterases (PDEs) mediate the hydrolysis of second messengers, cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). There are 11 gene superfamilies that encode PDEs, comprising various genes (coding for subtypes A, B, C, etc.). These genes also generate alternative mRNA-splicing variants, resulting in around 100 different PDE isoforms [91].

Although there may be some functional redundancy among isoenzymes, most PDE isoforms and variants play specific physiological roles in mammalian cells. This provides an opportunity to create PDE4 inhibitors that target specific subtypes for varied conditions, aiming at optimize effectiveness and tolerance characteristics. Over the past ten years, evidence has grown indicating that PDE4 might have a significant role in fibrosis, supported by animal studies and *in vitro* experiments, examining the impact of PDE4 inhibitors on fibroblasts functionality. The effectiveness of PDE4 inhibitors in reducing lung fibrosis has been observed across diverse experimental setups, notably in rodents experiencing bleomycin-induced fibrosis. In rat models, demonstrated reduction of Ashcroft fibrosis score, hydroxyproline levels, and serum tumour necrosis factor-α (TNF-α) [92,93]. Improvement of lung fibrosis by PDE4 inhibition was not limited to TGF-B1 effects, have been shown to directly influence various functions of fibroblasts in human-derived fibroblast cell lines. Kohyama et al. [94] illustrated the direct impact of PDE4 inhibitors on fibroblasts *in vitro*. In human foetal lung fibroblasts (HFL-1), both rolipram and cilomilast hindered FN-induced chemotaxis and the contraction of collagen gels. The

Table 1. Most recent phase 3 randomized clinical trials on pharmacotherapies for Idiopathic Pulmonary Fibrosis (IPF)

Molecule	Mechanism of Action	Route of Administration	Primary Outcome	Status	ClinicalTrial.Gov Identifier
Zirtaxestat	Selective Autotaxin inhibitor	Oral	Annual Rate of Decline in FVC up to Week 52	Terminated: early discontinuation after interim analysis revealed the increased mortality in the patients group receiving a 600 mg daily dose and a lack of efficacy in all the treatment groups	NCT03711162; NCT03733444
BMS-873786	LPA receptor 1 antagonist	Oral	Absolute change from baseline in forced vital capacity (FVC) measured in mL [to week 52]	Ongoing	NCT06003426
Pamrevlumab	Humanized monoclonal antibody targeting the Connective Tissue Growth Factor (CTGF)	Intravenous	Change From Baseline in Forced Vital Capacity (FVC) at Week 48	Terminated: Zephyrus I did not meet primary endpoint and, based on its results, Zephyrus II has been discontinuated	NCT03955146, NCT04419558
Recombinant Human Pentraxin-2 (rhPTX-2; PRM-151)	Inhibition of TGF-β1 production and differentiation of monocytes into profibrotic fibrocytes	Intravenous	Absolute Change in Forced Vital Capacity (FVC [mL]) [from baseline to week 52]	Terminated: futility analysis outcome indicated that the study was unlikely to meet the predefined primary objective of the study. No new safety concerns were identified.	NCT04552899
Treprostinil	Prostacyclin analogue	Inhalatory	Change in Absolute FVC from Baseline to Week 52	Ongoing	NCT05255991
BI 1015550	Phosphodiesterase 4B (PDE4B) inibitor	Oral	Absolute change from baseline in Forced Vital Capacity (FVC) (mL) at Week 52	Complete (enrollment concluded in June 2023)	NCT05321069
N-acetylcysteine (NAC)	Antioxidant effect tested in a selected cohort of IPF patients with a TOLLIP rs3750920 TT genotype	Oral	Time to one of the following composite endpoint criteria: 10% relative decline in forced vital capacity (FVC), first respiratory hospitalization, lung transplant or death from any cause.	Ongoing	NCT04300920

inhibitory effect of prostaglandin E2 (PGE2) on fibroblast function was enhanced in the presence of PDE4 inhibitors, and the impact of these inhibitors was reduced when endogenous PGE2 was blocked by indomethacin.

BI 1015550, an oral inhibitor, exhibits preferential targeting of PDE4B with around 10 times greater selectivity for inhibiting PDE4B compared to other PDE4 [95] .

FIBRONEER-IPF is a phase III, double blind, randomized, clinical trial conducted across multiple centres worldwide, using a placebo-controlled design. It aims to assess the effectiveness and safety of BI 1015550 in IPF patients, categorized by their utilization of antifibrotic treatments, spanning a period of at least 52 weeks (NCT05321069). The primary endpoint is absolute change from baseline in FVC (mL) at week 52. Started in September 2022, the trial completed its enrolment in June 2023. The intended enrolment targets 963 patients, randomized evenly in a 1:1:1 ratio to receive either 9 mg or 18 mg of BI 1015550 or a placebo administered twice daily. Moreover, the patients have been stratified based on their background use of antifibrotic treatments during screening [96]. The population of included patients is approximately equivalent to those in all the other previously described trials, with minor variations in the FVC and DL_{CO} cut-off values.

Encouraging data came from the phase 2 trial of Fibroneer-IPF that shows among patients without background antifibrotic use, the median change in the FVC was 5.7 mL (95% CI, -39.1 to 50.5) in the BI group and -81.7 mL (95% CI, -133.5 to -44.8) in the placebo group. Among patients with background antifibrotic use, the median change in the FVC was 2.7 ml (95% CI, -32.8 to 38.2) in the BI 1015550 group and -59.2 ml (95% CI, -111.8 to -17.9) in the placebo group (median difference, 62.4 ml; 95% CI, 6.3 to 125.5; probability that BI 1015550 was superior to placebo, 0.986)[97] . Preclinical research indicates that BI 1015550 exhibits complementary actions to nintedanib concerning the transformation of human myofibroblasts and, when used together, they have a synergistic impact on fibroblast proliferation [95,98]. This data leads us to hope for the future possibility of using multiple drugs in synergy to target different pathways simultaneously. On the other hand, the most frequently encountered side effect with PDE4B is diarrhea [97]. Unfortunately, nintedanib commonly presents the same side effect [9], suggesting that in clinical practice, combining the two might be compromised by this common adverse event. Hence, studies and strategies will be necessary to address this possibility and ensure maximum patient adherence to the therapy.

Market-available oral PDE4 inhibitors are linked to side effects such as depression, thoughts of suicide, and related behaviors [99]. During Phase II there was just one report of suicidal ideation that occurred after the residual effect period of BI 1015550 [97]. If the drug will be approved, higher attention in daily clinical practice will be required, in daily clinical practice, to the anxiety/depression and suicidal behavior aspect, conditions that in their reactive form are often associated with idiopathic pulmonary fibrosis [100]. A unique example of a strategy to address anxiety/depression disorder is the one proposed by G. D. Edwards et al. demonstrating a significant reduction in the HADS (Hospital Anxiety and Depression Scale) score through respiratory rehabilitation [101].

IPF is associated with significant risk of comorbidities that may differently influence the prognosis of patients [102]. Pulmonary Hypertension (PH) frequently complicates the course of patients with IPF, with a reported wide prevalence range of 10%–86% [103]. One study demonstrated that IPF patients with PH documented via right heart catheterization had a 1-year mortality of 28% versus those without PH, whose 1-year mortality was only 5.5% [104]. For a long time, it was believed that pulmonary hypertension in idiopathic pulmonary fibrosis (IPF) was caused by the narrowing of blood vessels due to low oxygen and damage to the lung's capillary network from fibrosis. Although these factors probably play a role in the development of pulmonary hypertension in IPF, recent evidences show that other mechanisms are also involved [105]. Drugs approved for pulmonary arterial hypertension have been investigated in several randomized controlled trials in PH-ILD patients, leading to discouraging results until the recent INCREASE study [106–109]. Among individuals suffering from pulmonary hypertension caused by interstitial lung disease, the use of inhaled treprostinil

resulted in enhanced exercise capacity compared to the initial level, as evaluated through a 6-minute walk test [109]. Treprostinil is a stable analogue of prostacyclin, which promotes vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation [110]. The INCREASE study was a 16-week research conducted across multiple centers, employing randomization, a double-blind methodology, and a placebo-controlled approach. It aimed to evaluate the safety and effectiveness of inhaled treprostinil in 326 individuals diagnosed with PH-ILD, which includes pulmonary hypertension associated with idiopathic pulmonary fibrosis (IPF) [109]. Apart from achieving the primary goal of assessing the 6-minute walk distance (6MWD) and secondary endpoints, *post hoc* analysis of the INCREASE study revealed that inhaled treprostinil led to notable enhancements in forced vital capacity (FVC) among PH-ILD subjects [111]. Furthermore, when focusing on patients with IPF, FVC improvements of 84.5 mL (SE 52.7; 95% CI −20.4 to 189.5; p=0.11) by week 8 and 168.5 mL (SE 64.5; 95% CI 40.1 to 297.0; p=0.011) by week 16 were observed. There was also a significant reduction in acute disease exacerbations among the IPF patient group compared to the placebo. The enhancements in forced vital capacity (FVC) and the reduction in exacerbations related to the underlying lung condition, as observed in the INCREASE study, indicate that inhaled treprostinil could represent a viable treatment choice for individuals diagnosed with IPF.

Based on these findings, a phase 3 randomized clinical trial, TETON, has been launched as the first clinical trial investigating an inhaled therapy specifically designed for IPF. TETON (NCT04708782) will be a 52-week, randomized, double-blind placebo-controlled, phase 3 study with a nebulized solution of treprostinil in patients with IPF. All subjects will initiate to inhale treprostinil (6 μg/breath) or placebo at a dose of 3 breaths (18 μg) administered four times daily (during waking hours) and will titrate to a target dosing regimen of 12 breaths (72 μg) four times daily. Administering the treatment directly to the lungs might potentially offer added advantages with fewer adverse effects when compared to systemic therapy. This trial aims to investigate the use of inhaled treprostinil in a manner that closely mirrors real-world treatment for IPF by avoiding unnecessary restrictions in the inclusion and exclusion criteria, unlike other IPF studies. Notably, there is not an upper age limit, individuals on the lung transplant list are eligible for participation, and the forced vital capacity (FVC) requirement is set at ≥45% (with no upper limit). Patients may also undergo background therapy with pirfenidone or nintedanib, provided they have been on a stable and optimized dose for a minimum of 30 days before the baseline assessment. Like previous trials, the primary endpoint is the reduction of FVC over 52 weeks. [112] The potential success of the trial could lead to the approval of the first "topical" therapy in IPF, consequently offering a treatment with minimal systemic side effects.

Several interesting phase 2 studies are about to commence their recruitment, focusing on next-generation molecules belonging to the family of monoclonal antibodies, such as vixarelimab (NCT05785624), binding the beta subunit of the oncostatin M receptor, now approved for the treatment of chronic *Prurigo Nodularis* [113] and axatilimab (NCT06132256) directed to colony stimulating factor-1 receptor (CSF-1R), targeting pathways mediated by profibrotic macrophages, that was already demonstrated to be a promising novel treatment strategy for refractory chronic Graft-Versus-Host-Disease [114]. At present, it is not possible to comment on the data and rationale behind these studies as they are still confidential to the sponsoring entities. It will be necessary to wait for the conclusion of these studies to analyze the initial results of these promising new molecules.

The most forward-looking trial stems from a careful observation of the past in IPF therapy. We have previously mentioned the PANTHER study, which demonstrated the failure of combination therapy involving azathioprine, prednisone, and NAC [30]. However, a *post hoc* analysis revealed a potential beneficial effect of NAC in a subgroup of individuals carrying a specific genetic variant, the TOLLIP rs3750920 TT genotype, present in about 25% of patients with IPF [115]. Those patients had a significant reduction of hospitalization, death, transplant, <10% FVC decline compared with those who received placebo. Those with TOLLIP CT genotype (50% of cohort) had similar outcomes to those treated with placebo.

In contrast, the population with the TOLLIP CC genotype (25% of the cohort) indicated a trend for unfavorable outcomes with NAC treatment [115]. The TOLLIP gene encodes a ubiquitin-binding protein, regulating the innate immune response by inhibiting Toll-like receptor (TLR) signaling. TLRs are pivotal in the innate immune response against diverse pathogen-associated molecular patterns. Changes in TLR expression and signaling have been associated with the progression and mortality of IPF [115–117] .

In PRECISIONS-IPF, a phase 3, multi-center, randomized, double-blind, placebo-controlled trial the patients will be selected, for the first time in IPF Trial, by genotyping (NCT04300920). Patient with TOLLIP rs3750920 TT genotype, while receiving standard of care, will be randomized to NAC (600 mg tablets to be taken three times a day) or placebo in a 1:1 ratio and will last 24 months. The study is also at the forefront for its trial procedures; in fact, patients will be offered the opportunity to participate in monitoring through home spirometry three times a week in the morning using a portable spirometer. In well-trained patients, home spirometry has proven to be a reliable tool in monitoring the progression of IPF [118]. The economic aspect of the potential approval of NAC in this population should not be underestimated. A recent published systematic review has shown that NAC + pirfenidone were the most efficacious, tolerable and cost-effective therapy in IPF [119].

The precision medicine approach is still lacking in pulmonary fibrosis, patients with IPF have highly heterogenous clinical trajectories, and prognosis for each individual patient is difficult to predict. These key differences among patients suggest that subgroups of patients may respond differently to treatments.

Another opportunity for IPF therapy is to optimize treatments already approved by exploring alternative administration routes. Pirfenidone stands as the first antifibrotic that received worldwide approval for IPF therapy [120]. Patients undergoing oral pirfenidone therapy may commonly experience gastrointestinal side effects and skin rashes, leading both physician and patient to consider switching to nintedanib or discontinuing antifibrotic treatment [121]. Considering this, a phase 1b trial (AP01-002 ACTRN12618001838202) comparing the safety and tolerability of nebulized AP01 (a novel formulation of inhaled pirfenidone) 50 mg once daily or 100 mg two twice a day has been proposed to evaluate differences in terms of safety of same molecule with different routes of administration. The most common treatment-related adverse events (frequency, % of patients) were all mild or moderate and included cough (14, 15.4%), rash (11, 12.1%), nausea (8, 8.8%), throat irritation (5, 5.5%), fatigue (4, 4.4%) and taste disorder, dizziness and dyspnea (three each, 3.3%). Side effects commonly associated with oral pirfenidone in other clinical trials were less frequent with AP01 [122] .

Research has not focused only on drugs able to target specific pathways involved in the typical progressive scarring of lungs, but also on some important aspects like symptoms and particularly chronic cough [123]), that represents an important cause of quality of life impairment. In IPF cough does not show a clear correlation with pulmonary function, in addition there are some evidence showing an heightened cough reflex sensitivity in this patients and a decrease in cough frequency during sleep suggesting a neurological involvement [127] [128]. Gefapixant, a P2X3 receptor antagonist, has been investigated in patients with treatment-resistant and unexplained chronic cough; unfortunately, it did not meet the pre-specified primary objective of reduction in awake cough frequency [129] . Mixed opioid agonists/antagonists can reduce chronic cough by pharmacologically acting on the opioid system potentially at both peripheral and central nervous system levels [130]. An interim analysis of phase 2 data indicates that NAL ER (Nalbuphine Extended Release) is the first therapy with a significant reduction in IPF-related hourly daytime chronic cough frequency [131]. Based on this evidence a phase 2b trial will commence recruitment in 2024 to confirm and strengthen these findings (NCT05964335).

Another relevant therapeutic issue related to IPF is the treatment of acute exacerbations, dramatic events marked by a rapid clinical and radiological worsening that may lead to death. Unfortunately, there are not effective treatments for patients experiencing acute exacerbation, with only retrospective series providing evidence. Consequently, therapeutic approaches for these patients are often anecdotal or based on personal experience [132]. The 2011 international guidelines on

IPF recommended glucocorticoids for most cases of acute exacerbation; however, this was a weak recommendation relying on expert opinion [120]. Results from EXAFIP trial clarify that cyclophosphamide added to glucocorticoids in AE-IPFs increase 3 months mortality [133]. In 2021 Tejaswini et al. proposed a triple therapy strategy for autoantibody reduction in acute exacerbations, combining therapeutic plasma exchanges (TPE), two doses of rituximab, and four intravenous immunoglobulin (IVIG) infusion. This article shows that this association is related to an improvement in gas exchange, rapid response to therapies, and cumulative one year survival. The data should be assessed with the caveat that the cited study lacked a control cohort [134]. For these reasons, a clinical trial (STRIVE-IPF) is currently recruiting to test this triple therapy with the methodological rigor of randomization placebo/control cohort (NCT03286556).

Conclusion

Pharmacological treatment of IPF remains one the most challenging aspect in the field of ILDs and the entire respiratory medicine. The efforts made by the scientific community in the past led to efficient drugs able to slow down the decline typical of the disease, but it is not enough considering its still unfortunate prognosis. Preclinical studies to better understand the mechanisms underlying this condition are still needed. Meantime, the proposal of several new molecules and the recent new insights in the design of clinical trials represent the basics of promising future results.

References

1. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Antoniou KM, Bissell BD, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. https://doi.org/10.1164/rccm.202202-0399ST 2022, 205, E18–E47, doi:10.1164/RCCM.202202-0399ST.
2. Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global Incidence and Prevalence of Idiopathic Pulmonary Fibrosis. Respir Res 2021;22:197. doi:10.1186/s12931-021-01791-z.
3. Ley B, Collard HR, King TE. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2011;183:431-40, doi:10.1164/RCCM.201006-0894CI.
4. Salonen J, Purokivi M, Bloigu R, Kaarteenaho R. Prognosis and Causes of Death of Patients with Acute Exacerbation of Fibrosing Interstitial Lung Diseases. BMJ Open Respir Res 2020;7. doi:10.1136/bmjresp-2020-000563.
5. Kim HJ, Perlman D, Tomic R. Natural History of Idiopathic Pulmonary Fibrosis. Respir Med 2015;109:661-70. doi:10.1016/j.rmed.2015.02.002.
6. Torrisi SE, Ley B, Kreuter M, Wijsenbeek M, Vittinghoff E, Collard HR, et al. The Added Value of Comorbidities in Predicting Survival in Idiopathic Pulmonary Fibrosis: A Multicentre Observational Study. Eur Respir J 2019;53:1801587. doi:10.1183/13993003.01587-2018.
7. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44–e68. doi:10.1164/RCCM.201807-1255ST.
8. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomised Trials. Lancet 2011;377:1760-69. doi:10.1016/S0140-6736(11)60405-4.
9. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med 2014;370:2083-92. doi:10.1056/NEJMOA1402582.
10. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. New Engl J Med 2014;370:2071-82. doi:10.1056/NEJMOA1402584/
11. Mondoni M, Varone F, Alfano F, Muscato G, Conti C, Saderi L, et al. Predictors of Stability/Improvement of Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis After One Year of Treatment With Nintedanib. Arch Bronconeumol 2023;59:464-66. doi:10.1016/j.arbres.2023.02.010.
12. Richeldi L, Collard HR, Jones MG. Idiopathic Pulmonary Fibrosis. Lancet 2017;389:1941-52. doi:10.1016/S0140-6736(17)30866-8.
13. Wynn TA. Integrating Mechanisms of Pulmonary Fibrosis. J Exp Med 2011;208:1339-50. doi:10.1084/JEM.20110551.
14. Wilson MS, Wynn TA. Pulmonary Fibrosis: Pathogenesis, Etiology and Regulation. Mucosal Immunol 2009;2:103. doi:10.1038/MI.2008.85.
15. Zaman T, Lee JS. Risk Factors for the Development of Idiopathic Pulmonary Fibrosis: A Review. Curr Pulmonol Rep 2018;7:118-25. doi:10.1007/s13665-018-0210-7.
16. Spagnolo P, Cottin V. Genetics of Idiopathic Pulmonary Fibrosis: From Mechanistic Pathways to Personalised Medicine. J Med Genet 2017;54:93-9. doi:10.1136/jmedgenet-2016-103973.

17. Kropski JA, Blackwell TS. Progress in Understanding and Treating Idiopathic Pulmonary Fibrosis. Ann Rev Med 2019;70:211-24. doi:10.1146/annurev-med-041317-102715.
18. Fernandez IE, Eickelberg O. The Impact of TGF-β on Lung Fibrosis: From Targeting to Biomarkers. Proc Am Thorac Soc 2012;9:111-16. doi:10.1513/PATS.201203-023AW.
19. Mora AL, Rojas M, Pardo A, Selman M. Emerging Therapies for Idiopathic Pulmonary Fibrosis, a Progressive Age-Related Disease. Nat Rev Drug Discov 2017;16:755-72. doi:10.1038/nrd.2017.170.
20. McAnulty RJ, Laurent GJ. Pathogenesis of Lung Fibrosis and Potential New Therapeutic Strategies. Exp Nephrol 1995;2:96-107.
21. Meier-Sydow J, Rust M, Kronenberger H, Thiel C, Amthor M, Riemann H. [Long-Term Follow-up of Lung Function Parameters in Patients with Idiopathic Pulmonary Fibrosis Treated with Prednisone and Azathioprin or d-Penicillamine (Author's Transl)]. Prax Klin Pneumol 1979;33(Suppl 1):680-88.
22. Meier-Sydow J, Weiss SM, Buhl R, Rust M, Raghu G. Idiopathic Pulmonary Fibrosis: Current Clinical Concepts and Challenges in Management. Semin Respir Crit Care Med 1994;15:77-96. doi:10.1055/S-2007-1006351/BIB.
23. Raghu G, Depaso WJ, Cain K, Hammar SP, Wetzel CE, Dreis DF, et al. Azathioprine Combined with Prednisone in the Treatment of Idiopathic Pulmonary Fibrosis: A Prospective Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Am Rev Respir Dis 1991;144:291-96. doi:10.1164/AJRCCM/144.2.291.
24. Johnson MA, Kwan S, Snell NJC, Nunn AJ, Darbyshire JH, Turner-Warwick, et al. Randomised Controlled Trial Comparing Prednisolone Alone with Cyclophosphamide and Low Dose Prednisolone in Combination in Cryptogenic Fibrosing Alveolitis. Thorax 1989;44:280-88. doi:10.1136/THX.44.4.280.
25. Douglas WW, Ryu JH, Swensen SJ, Offord KP, Schroeder DR, Caron GM, et al. Colchicine versus Prednisone in the Treatment of Idiopathic Pulmonary Fibrosis. A Randomized Prospective Study. Members of the Lung Study Group. Am J Respir Crit Care Med 1998;158:220-25. doi:10.1164/AJRCCM.158.1.9709089.
26. Peters SG, McDougall JC, Douglas WW, Coles DT, DeRemee RA. Colchicine in the Treatment of Pulmonary Fibrosis. Chest 1993;103:101-4: doi:10.1378/CHEST.103.1.101.
27. Rennard SI, Bitterman PB, Ozaki T, Rom WN, Crystal RG. Colchicine Suppresses the Release of Fibroblast Growth Factors from Alveolar Macrophages in Vitro. The Basis of a Possible Therapeutic Approach Ot the Fibrotic Disorders. Am Rev Respir Dis 1988;137:181-5. doi:10.1164/AJRCCM/137.1.181.
28. King J, Costabel U, Cordier JF, DoPico GA, DuBois RM, Lynch D, et al. American Thoracic Society. Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. International Consensus Statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646-64. doi:10.1164/AJRCCM.161.2.ATS3-00.
29. Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, et al. High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis. N Engl J Med 2005;353:2229-42. doi:10.1056/NEJMOA042976.
30. Idiopathic Pulmonary Fibrosis Clinical Research Network; Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. N Engl J Med 2012;366:1968-77. doi:10.1056/NEJMoa1113354.
31. Wen FQ, Liu XD, Terasaki Y, Fang QH, Kobayashi T, Abe S, et al. Interferon-γ Reduces Interleukin-4- and Interleukin-13-Augmented Transforming Growth Factor-B2 Production in Human Bronchial Epithelial Cells by Targeting Smads. Chest 2003;123:372S-373S. doi:10.1016/S0012-3692(15)35217-X.
32. Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH. A Preliminary Study of Long-Term Treatment with Interferon Gamma-1b and Low-Dose Prednisolone in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med 1999;341:1264-9. doi:10.1056/NEJM199910213411703.
33. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A Placebo-Controlled Trial of Interferon Gamma-1b in Patients with Idiopathic Pulmonary Fibrosis. https://doi.org/10.1056/NEJMoa030511 2004, 350, 125–133, doi:10.1056/NEJMOA030511.
34. King TE, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, et al. Effect of Interferon Gamma-1b on Survival in Patients with Idiopathic Pulmonary Fibrosis (INSPIRE): A Multicentre, Randomised, Placebo-Controlled Trial. Lancet 2009;374:222-8. doi:10.1016/S0140-6736(09)60551-1.
35. Shi-Wen X, Denton CP, Dashwood MR, Holmes AM, Bou-Gharios G, Pearson JD, et al. Fibroblast Matrix Gene Expression and Connective Tissue Remodeling: Role of Endothelin-1. J Investig Derm 2001;116:417-25. doi:10.1046/J.1523-1747.2001.01256.X.
36. Park SH, Saleh D, Giaid A, Michel RP. Increased Endothelin-1 in Bleomycin-Induced Pulmonary Fibrosis and the Effect of an Endothelin Receptor Antagonist. Am J Respir Crit Care Med 1997;156:600-8. doi:10.1164/AJRCCM.156.2.9607123.
37. Ross B, D'Orléans-Juste P, Giaid A. Potential Role of Endothelin-1 in Pulmonary Fibrosis. https://doi.org/10.1165/rcmb.2009-0175TR2012,42,16–20,doi:10.1165/RCMB.2009-0175TR.
38. Fonseca C, Abraham D, Renzoni EA. Endothelin in Pulmonary Fibrosis. Am J Respir Cell Mol Biol 2011;44:1-10. doi:10.1165/RCMB.2009-0388TR.
39. King TE, Behr J, Brown KK, Du Bois RM, Lancaster L, De Andrade J.A, et al. BUILD-1: A Randomized Placebo-Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis. https://doi.org/10.1164/rccm.200705-732OC 2012, 177, 75–81, doi:10.1164/RCCM.200705-732OC.

40. King TE, Brown KK, Raghu G, Du Bois RM, Lynch DA, Martinez F, et al. BUILD-3: A Randomized, Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis. https://doi.org/10.1164/rccm.201011-1874OC 2012, 184, 92–99, doi:10.1164/RCCM.201011-1874OC.
41. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, et al. Treatment of Idiopathic Pulmonary Fibrosis with Ambrisentan: A Parallel, Randomized Trial. Ann Intern Med 2013;158:641-9. doi:10.7326/0003-4819-158-9-201305070-00003.
42. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J, Goh N, et al. Macitentan for the Treatment of Idiopathic Pulmonary Fibrosis: The Randomised Controlled MUSIC Trial. Eur Respir J 2013;42:1622-32. doi:10.1183/09031936.00104612.
43. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, et al. Sildenafil for Treatment of Lung Fibrosis and Pulmonary Hypertension: A Randomised Controlled Trial. Lancet 2002;360:895-900. doi:10.1016/S0140-6736(02)11024-5.
44. Idiopathic Pulmonary Fibrosis Clinical Research Network; Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis. N Engl J Med 2010;363:620-8. doi:10.1056/NEJMoa1002110.
45. Iyer SN, Margolin SB, Hyde DM, Giri SN. Lung Fibrosis Is Ameliorated by Pirfenidone Fed in Diet after the Second Dose in a Three-Dose Bleomycin-Hamster Model. Exp Lung Res 1998;24:119-33. doi:10.3109/01902149809046058.
46. Molina-Molina M, Machahua-Huamani C, Vicens-Zygmunt V, Llatjós R, Escobar I, Sala-Llinas E, et al. Anti-Fibrotic Effects of Pirfenidone and Rapamycin in Primary IPF Fibroblasts and Human Alveolar Epithelial Cells. BMC Pulm Med 2018;18. doi:10.1186/S12890-018-0626-4.
47. Jin J, Togo S, Kadoya K, Tulafu M, Namba Y, Iwai M, et al. Pirfenidone Attenuates Lung Fibrotic Fibroblast Responses to Transforming Growth Factor-B1. Respir Res 2019;20. doi:10.1186/S12931-019-1093-Z.
48. Raghu G, Johnson, WC, Lockhart D, Mageto Y. Treatment of Idiopathic Pulmonary Fibrosis with a New Antifibrotic Agent, Pirfenidone: Results of a Prospective, Open-Label Phase II Study. Am J Respir Crit Care Med 1999;159:1061-9. doi:10.1164/AJRCCM.159.4.9805017.
49. Nagai S, Hamada K, Shigematsu M, Taniyama M, Yamauchi S, Izumi T. Open-Label Compassionate Use One Year-Treatment with Pirfenidone to Patients with Chronic Pulmonary Fibrosis. Internal Med 2002;41:1118-23. doi:10.2169/INTERNALMEDICINE.41.1118.
50. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-Blind, Placebo-Controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2005;171:1040-7. doi:10.1164/RCCM.200404-571OC.
51. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga MT, et al. Pirfenidone in Idiopathic Pulmonary Fibrosis. Eur Respir J 2010;35:821-9. doi:10.1183/09031936.00005209.
52. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomised Trials. Lancet 2011;377:1760-9. doi:10.1016/S0140-6736(11)60405-4.
53. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. New England J Med 2014;370:2083-92. doi:10.1056/NEJMOA1402582.
54. Noble PW, Albera C, Bradford WZ, Costabel U, Bois RMD, Fagan EA, et al. Pirfenidone for Idiopathic Pulmonary Fibrosis: Analysis of Pooled Data from Three Multinational Phase 3 Trials. Eur Respir J 2016;47:243-53. doi:10.1183/13993003.00026-2015.
55. Cottin V, Maher T. Long-Term Clinical and Real-World Experience with Pirfenidone in the Treatment of Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2015;24:58-64. doi:10.1183/09059180.00011514.
56. Gulati S, Luckhardt TR. Updated Evaluation of the Safety, Efficacy and Tolerability of Pirfenidone in the Treatment of Idiopathic Pulmonary Fibrosis. Drug Healthc Patient Saf 2020;12:85-94. doi:10.2147/DHPS.S224007.
57. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, et al. Pirfenidone Safety and Adverse Event Management in Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2017;26. doi:10.1183/16000617.0057-2017.
58. Garneau-Tsodikova S, Thannickal V. Protein Kinase Inhibitors in the Treatment of Pulmonary Fibrosis. Curr Med Chem 2008;15:2632-40. doi:10.2174/092986708785908969.
59. Buchdunger E, O'Reilly T, Wood J. Pharmacology of Imatinib (STI571). Eur J Cancer 2002;38:S28–S36. doi:10.1016/S0959-8049(02)80600-1.
60. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR, et al. Imatinib Treatment for Idiopathic Pulmonary Fibrosis: Randomized Placebo-Controlled Trial Results. Am J Respir Crit Care Med 2010;181:604-10. doi:10.1164/RCCM.200906-0964OC.
61. Chaudhary NI, Roth GJ, Hilberg F, Müller-Quernheim J, Prasse A, Zissel G, et al. Inhibition of PDGF, VEGF and FGF Signalling Attenuates Fibrosis. Eur Respir J 2007;29:976-85. doi:10.1183/09031936.00152106.
62. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and Anti-Inflammatory Activity of the Tyrosine Kinase Inhibitor Nintedanib in Experimental Models of Lung Fibrosis. J Pharmac Exper Ther 2014;349:209-20. doi:10.1124/JPET.113.208223.
63. Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: Triple Angiokinase Inhibitor with Sustained

Receptor Blockade and Good Antitumor Efficacy. Cancer Res 2008;68:4774-82. doi:10.1158/0008-5472.CAN-07-6307.
64. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis. N Engl J Med 2011;365:1079-87. doi:10.1056/NEJMOA1103690.
65. Vancheri C, Kreuter M, Richeldi L, Ryerson CJ, Valeyre D, Grutters JC, et al. Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis: Results of the INJOURNEY Trial. Am J Respir Crit Care Med 2018;197:356-63. doi:10.1164/RCCM.201706-1301OC.
66. Https://Www.Clinicaltrials.Gov/.
67. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue, Y Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022;205:e18-e47. doi:10.1164/rccm.202202-0399ST.
68. Zulfikar S, Mulholland,S, Adamali H, Barratt SL. Inhibitors of the Autotaxin-Lysophosphatidic Acid Axis and Their Potential in the Treatment of Interstitial Lung Disease: Current Perspectives. Clin Pharmacol 2020;2:97-108. doi:10.2147/CPAA.S228362.
69. Tager AM, LaCamera P, Shea BS, Campanella GS, Selman M, Zhao Z, et al. The Lysophosphatidic Acid Receptor LPA1 Links Pulmonary Fibrosis to Lung Injury by Mediating Fibroblast Recruitment and Vascular Leak. Nat Med 2008;14:45-54. doi:10.1038/nm1685.
70. Oikonomou N, Mouratis MA, Tzouvelekis A, Kaffe E, Valavanis C, Vilaras G, et al. Pulmonary Autotaxin Expression Contributes to the Pathogenesis of Pulmonary Fibrosis. Am J Respir Cell Mol Biol 2012;47:566-74. doi:10.1165/rcmb.2012-0004OC.
71. Ninou I, Magkrioti C, Aidinis V. Autotaxin in Pathophysiology and Pulmonary Fibrosis. Front Med (Lausanne) 2018;5. doi:10.3389/fmed.2018.00180.
72. Maher TM, van der Aar EM, Van de Steen O, Allamassey L, Desrivot J, Dupont S, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GLPG1690, a Novel Autotaxin Inhibitor, to Treat Idiopathic Pulmonary Fibrosis (FLORA): A Phase 2a Randomised Placebo-Controlled Trial. Lancet Respir Med 2018;6:627-35. doi:10.1016/S2213-2600(18)30181-4.
73. Maher TM, Ford P, Brown KK, Costabel U, Cottin V, Danoff SK, et al. Ziritaxestat, a Novel Autotaxin Inhibitor, and Lung Function in Idiopathic Pulmonary Fibrosis. JAMA 2023;329:1567. doi:10.1001/jama.2023.5355.
74. Gill MW, Lakshmi S, Cheng PTW, Murphy BJ, Chadwick K, Lehman-McKeeman L, et al. BMS-986278, an LPA1 Receptor Antagonist for Idiopathic Pulmonary Fibrosis: Preclinical Assessments of Potential Hepatobiliary Toxicity, American Thoracic Society 2019; A5882-A5882.
75. Corte TJ, Lancaster L, Swigris JJ, Maher TM, Goldin JG, Palmer SM, et al. Phase 2 Trial Design of BMS-986278, a Lysophosphatidic Acid Receptor 1 (LPA_1) Antagonist, in Patients with Idiopathic Pulmonary Fibrosis (IPF) or Progressive Fibrotic Interstitial Lung Disease (PF-ILD). BMJ Open Respir Res 2021;8:e001026. doi:10.1136/bmjresp-2021-001026.
76. Corte TJ, Cottin V, Glassberg MK, Kreuter M, Ogura T, Suda T, et al. BMS-986278, an Oral Lysophosphatidic Acid Receptor 1 (LPA1) Antagonist, for Patients With Idiopathic Pulmonary Fibrosis: Results From a Phase 2 Randomized Trial, American Thoracic Society 2023;A2785-A2785.
77. Pelaia C, Crimi C, Vatrella A, Tinello C, Terracciano R, Pelaia G. Molecular Targets for Biological Therapies of Severe Asthma. Front Immunol 2020;11. doi:10.3389/fimmu.2020.603312.
78. Singh S, Kumar NK, Dwiwedi P, Charan J, Kaur R, Sidhu P, et al. Monoclonal Antibodies: A Review. Curr Clin Pharmacol 2018;13:85-99. doi:10.2174/1574884712666170809124728.
79. Lipson KE, Wong C, Teng Y, Spong S. CTGF Is a Central Mediator of Tissue Remodeling and Fibrosis and Its Inhibition Can Reverse the Process of Fibrosis. Fibrogenesis Tissue Repair 2012;5:S24. doi:10.1186/1755-1536-5-S1-S24.
80. Richeldi L, Fernández Pérez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, et al. Pamrevlumab, an Anti-Connective Tissue Growth Factor Therapy, for Idiopathic Pulmonary Fibrosis (PRAISE): A Phase 2, Randomised, Double-Blind, Placebo-Controlled Trial. Lancet Respir Med 2020;8:25-33. doi:10.1016/S2213-2600(19)30262-0.
81. FibroGen, I. FibroGen Announces Topline Results from Phase 3 ZEPHYRUS-1 Study of Pamrevlumab for the Treatment of Idiopathic Pulmonary Fibrosis.
82. Pilling D, Galvis-Carvajal E, Karhadkar TR, Cox N, Gomer RH. Monocyte Differentiation and Macrophage Priming Are Regulated Differentially by Pentraxins and Their Ligands. BMC Immunol 2017;18:30. doi:10.1186/s12865-017-0214-z.
83. Castaño AP, Lin SL, Surowy T, Nowlin BT, Turlapati SA, Patel T, et al. Serum Amyloid P Inhibits Fibrosis Through FcγR-Dependent Monocyte-Macrophage Regulation in Vivo. Sci Transl Med 2009;1. doi:10.1126/scitranslmed.3000111.
84. Raghu G, van den Blink, B, Hamblin, M.J, Brown, A.W, Golden, J.A, Ho, et al. Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis. JAMA 2018;319:2299. doi:10.1001/jama.2018.6129.
85. Podolanczuk AJ, Richeldi L, Martinez FJ. The Future of Clinical Trials in Idiopathic Pulmonary Fibrosis. JAMA 2023;329:1554. doi:10.1001/jama.2022.23955.
86. Martinez FJ, Yow E, Flaherty KR, Snyder LD, Durheim MT, Wisniewski SR, et al. Effect of Antimicrobial Therapy on Respiratory Hospitalization or Death in Adults With Idiopathic Pulmonary Fibrosis. JAMA 2021;325:1841. doi:10.1001/jama.2021.4956.

87. Raghu G, Ghazipura M, Fleming TR, Aronson KI, Behr J, Brown KK, et al. Meaningful Endpoints for Idiopathic Pulmonary Fibrosis (IPF) Clinical Trials: Emphasis on "Feels, Functions, Survives." Am J Respir Crit Care Med 2024;209(6):647-69. doi:10.1164/rccm.202312-2213SO.
88. Worndl E, Hunt EB, Kennedy MP, Henry MT, Plant BJ, Murphy DM. Roflumilast in COPD. Chest 2015;148:e31. doi:10.1378/CHEST.15-0664.
89. Gooderham M, Papp K. Selective Phosphodiesterase Inhibitors for Psoriasis: Focus on Apremilast. BioDrugs 2015;29:327-39. doi:10.1007/S40259-015-0144-3.
90. McDowell L, Olin B. Crisaborole: A Novel Nonsteroidal Topical Treatment for Atopic Dermatitis. J Pharm Technol 2019;35:172-78. doi:10.1177/8755122519844507.
91. Azevedo MF, Faucz FR, Bimpaki E, Horvath A, Levy I, de Alexandre RB, et al. Clinical and Molecular Genetics of the Phosphodiesterases (PDEs). Endocr Rev 2014;35:195-233. doi:10.1210/er.2013-1053.
92. Pan JB, Hou YH, Zhang GJ. Rolipram Attenuates Bleomycin A5-induced Pulmonary Fibrosis in Rats. Respirology 2009;14:975-82. doi:10.1111/j.1440-1843.2009.01606.x.
93. Cortijo J, Iranzo A, Milara X, Mata M, Cerdá-Nicolás M, Ruiz-Saurí A, et al. Roflumilast, a Phosphodiesterase 4 Inhibitor, Alleviates Bleomycin-induced Lung Injury. Br J Pharmacol 2009;156:534-44. doi:10.1111/j.1476-5381.2008.00041.x.
94. Kohyama T, Liu X, Wen FQ, Kobayashi T, Fang Q, Abe S, et al. Cytokines Modulate Cilomilast Response in Lung Fibroblasts. Clinical Immunology 2004;111:297-302. doi:10.1016/j.clim.2004.01.007.
95. Herrmann FE, Hesslinger C, Wollin L, Nickolaus P. BI 1015550 Is a PDE4B Inhibitor and a Clinical Drug Candidate for the Oral Treatment of Idiopathic Pulmonary Fibrosis. Front Pharmacol 2022;13. doi:10.3389/fphar.2022.838449.
96. Richeldi L, Azuma A, Cottin V, Kreuter M, Maher TM, Martinez FJ, et al. Design of a Phase III, Double-Blind, Randomised, Placebo-Controlled Trial of BI 1015550 in Patients with Idiopathic Pulmonary Fibrosis (FIBRONEER-IPF). BMJ Open Respir Res 2023;10:e001563. doi:10.1136/bmjresp-2022-001563.
97. Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, et al. Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis. New England J Med 2022;386:2178-87. doi:10.1056/NEJMoa2201737.
98. Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, et al. Additive Effect of BI 1015550 and Nintedanib in Patients with IPF. In Proceedings of the 12.01 - Idiopathic interstitial pneumonias; European Respiratory Society, September 4 2022;4606.
99. Cazzola M, Calzetta L, Rogliani P, Matera MG. The Discovery of Roflumilast for the Treatment of Chronic Obstructive Pulmonary Disease. Expert Opin Drug Discov 2016;11:733-44. doi:10.1080/17460441.2016.1184642.
100. Lee YJ, Choi SM, Lee YJ, Cho YJ, Yoon H Il; Lee JH, et al. Clinical Impact of Depression and Anxiety in Patients with Idiopathic Pulmonary Fibrosis. PLoS One 2017;12. doi:10.1371/JOURNAL.PONE.0184300.
101. Edwards GD, Polgar O, Patel S, Barker RE, Walsh JA, Harvey J, et al. Mood Disorder in Idiopathic Pulmonary Fibrosis: Response to Pulmonary Rehabilitation. ERJ Open Res 2023;9. doi:10.1183/23120541.00585-2022.
102. Torrisi SE, Vancheri A, Pavone M, Sambataro G, Palmucci S, Vancheri C. Comorbidities of IPF: How Do They Impact on Prognosis. Pulm Pharmacol Ther 2018;53:6-11. doi:10.1016/J.PUPT.2018.09.003.
103. Nathan SD, King CS. Treatment of Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis: Shortfall in Efficacy or Trial Design? Drug Des Devel Ther 2014;8:875. doi:10.2147/DDDT.S64907.
104. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and Outcomes of Pulmonary Arterial Hypertension in Advanced Idiopathic Pulmonary Fibrosis. Chest 2006;129:746-52. doi:10.1378/CHEST.129.3.746.
105. Nikkho SM, Richter MJ, Shen E, Abman SH, Antoniou K, Chung J, et al. Clinical Significance of Pulmonary Hypertension in Interstitial Lung Disease: A Consensus Statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative-Group 3 Pulmonary Hypertension. Pulm Circ 2022;12. doi:10.1002/PUL2.12127.
106. Behr J, Nathan SD, Wuyts WA, Mogulkoc Bishop N, Bouros DE, Antoniou K, et al. Efficacy and Safety of Sildenafil Added to Pirfenidone in Patients with Advanced Idiopathic Pulmonary Fibrosis and Risk of Pulmonary Hypertension: A Double-Blind, Randomised, Placebo-Controlled, Phase 2b Trial. Lancet Respir Med 2021;9:85-95. doi:10.1016/S2213-2600(20)30356-8.
107. Nathan SD, Flaherty KR, Glassberg MK, Raghu G, Swigris J, Alvarez R, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis. Chest 2020;158:637-45. doi:10.1016/J.CHEST.2020.02.016.
108. Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez FJ, et al. Riociguat for Idiopathic Interstitial Pneumonia-Associated Pulmonary Hypertension (RISE-IIP): A Randomised, Placebo-Controlled Phase 2b Study. Lancet Respir Med 2019;7:780-90. doi:10.1016/S2213-2600(19)30250-4.
109. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med 2021;384:325-34. doi:10.1056/NEJMOA2008470.
110. Whittle BJ, Silverstein AM, Mottola DM, Clapp LH. Binding and Activity of the Prostacyclin Receptor (IP) Agonists, Treprostinil and Iloprost, at Human Prostanoid Receptors: Treprostinil Is a Potent DP1 and EP2 Agonist. Biochem Pharmacol 2012;84:68-75. doi:10.1016/J.BCP.2012.03.012.

111. Nathan SD, Waxman A, Rajagopal S, Case A, Johri S, DuBrock H, et al. Inhaled Treprostinil and Forced Vital Capacity in Patients with Interstitial Lung Disease and Associated Pulmonary Hypertension: A Post-Hoc Analysis of the INCREASE Study. Lancet Respir Med 2021;9:1266-74. doi:10.1016/S2213-2600(21)00165-X.
112. Nathan SD, Behr J, Cottin V, Lancaster L, Smith P, Deng CQ, et al. Study Design and Rationale for the TETON Phase 3, Randomised, Controlled Clinical Trials of Inhaled Treprostinil in the Treatment of Idiopathic Pulmonary Fibrosis. BMJ Open Respir Res 2022;9. doi:10.1136/BMJRESP-2022-001310.
113. Müller S, Zeidler C, Ständer S. Chronic Prurigo Including Prurigo Nodularis: New Insights and Treatments. Am J Clin Dermatol 2023;25(1):15-33. doi:10.1007/S40257-023-00818-Z.
114. Kitko CL, Arora M, Defilipp Z, Zaid MA, Di Stasi A, Radojcic V, et al. Axatilimab for Chronic Graft-Versus-Host Disease After Failure of at Least Two Prior Systemic Therapies: Results of a Phase I/II Study. J Clin Oncol 2023;41:1864-75. doi:10.1200/JCO.22.00958.
115. Oldham JM, Ma SF, Martinez FJ, Anstrom KJ, Raghu G, Schwartz DA, et al. TOLLIP, MUC5B, and the Response to N-Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2015;192:1475-82. doi:10.1164/RCCM.201505-1010OC.
116. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, et al. Genetic Variants Associated with Idiopathic Pulmonary Fibrosis Susceptibility and Mortality: A Genome-Wide Association Study. Lancet Respir Med 2013;1:309-17. doi:10.1016/S2213-2600(13)70045-6.
117. Trujillo G, Meneghin A, Flaherty KR, Sholl LM, Myers JL, Kazerooni EA, et al. TLR9 Differentiates Rapidly from Slowly Progressing Forms of Idiopathic Pulmonary Fibrosis. Sci Transl Med 2010;2. doi:10.1126/SCITRANSLMED.3001510.
118. Russell AM, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016;194:989-97. doi:10.1164/RCCM.201511-2152OC.
119. Zhao C, Yin Y, Zhu C, Zhu M, Ji T, Li Z, et al. Drug Therapies for Treatment of Idiopathic Pulmonary Fibrosis: A Systematic Review, Bayesian Network Meta-Analysis, and Cost-Effectiveness Analysis. EClinical Medicine 2023;61. doi:10.1016/J.ECLINM.2023.102071.
120. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med 2015;192:e3-e19. doi:10.1164/RCCM.201506-1063ST.
121. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, et al. Pirfenidone Safety and Adverse Event Management in Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2017;26. doi:10.1183/16000617.0057-2017.
122. West A, Chaudhuri N, Barczyk A, Wilsher ML, Hopkins P, Glaspole I, et al. Inhaled Pirfenidone Solution (AP01) for IPF: A Randomised, Open-Label, Dose-Response Trial. Thorax 2023;78(9):882-9. doi:10.1136/thorax-2022-219391.
123. Vigeland CL, Hughes AH, Horton MR. Etiology and Treatment of Cough in Idiopathic Pulmonary Fibrosis. Respir Med 2017;123:98-104. doi:10.1016/j.rmed.2016.12.016.
124. Biondini D, Balestro E, Sverzellati N, Cocconcelli E, Bernardinello N, Ryerson CJ, et al. Acute Exacerbations of Idiopathic Pulmonary Fibrosis (AE-IPF): An Overview of Current and Future Therapeutic Strategies. Expert Rev Respir Med 2020;14:405-14. doi:10.1080/17476348.2020.1724096.
125. Janowiak P, Szymanowska-Narloch A, Siemi-ska A. IPF Respiratory Symptoms Management — Current Evidence. Front Med (Lausanne) 2022;9. doi:10.3389/fmed.2022.917973.
126. Kondoh Y, Cottin V, Brown KK. Recent Lessons Learned in the Management of Acute Exacerbation of Idiopathic Pulmonary Fibrosis. Eur Respir Rev 2017;26:170050. doi:10.1183/16000617.0050-2017.
127. Key AL, Holt K, Hamilton A, Smith JA, Earis JE. Objective Cough Frequency in Idiopathic Pulmonary Fibrosis. Cough 2010;6. doi:10.1186/1745-9974-6-4.
128. Hope-Gill BDM, Hilldrup S, Davies C, Newton RP, Harrison NK. A Study of the Cough Reflex in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2003;168:995-1002. doi:10.1164/RCCM.200304-597OC.
129. Martinez FJ, Afzal AS, Smith JA, Ford AP, Li JJ, Li Y, et al. Treatment of Persistent Cough in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial. Pulm Ther 2021;7:471. doi:10.1007/S41030-021-00162-9.
130. Visca D, Beghè B, Fabbri LM, Papi A, Spanevello A. Management of Chronic Refractory Cough in Adults. Eur J Intern Med 2020;81. doi:10.1016/J.EJIM.2020.09.008.
131. Maher TM, Forbes W, Bortey E, Sciascia T. An Interim Analysis of a Phase 2 Trial Evaluating Oral Nalbuphine Extended Release for Treating Chronic Cough in Idiopathic Pulmonary Fibrosis. Eur Respir J 2022;60:4404. doi:10.1183/13993003.CONGRESS-2022.4404.
132. Churg A, Müller NL, Silva CIS, Wright JL. Acute Exacerbation (Acute Lung Injury of Unknown Cause) in UIP and Other Forms of Fibrotic Interstitial Pneumonias. Am J Surg Pathol 2007;31:277-84. doi:10.1097/01.PAS.0000213341.70852.9D.

133. Naccache JM, Jouneau S, Didier M, Borie R, Cachanado M, Bourdin A, et al. Cyclophosphamide Added to Glucocorticoids in Acute Exacerbation of Idiopathic Pulmonary Fibrosis (EXAFIP): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Lancet Respir Med 2022;10:26-34. doi:10.1016/S2213-2600(21)00354-4.

134. Kulkarni T, Valentine VG, Fei, F, Tran-Nguyen TK, Quesada-Arias LD, Mkorombindo T, et al. Correlates of Survival after Autoantibody Reduction Therapy for Acute IPF Exacerbations. PLoS One 2021;16. doi:10.1371/JOURNAL.PONE.0260345.

Received for publication: 24 April 2024 - Accepted for publication: 2 May 2024

Licensee Mattioli 1885, Italy
Multidisciplinary Respiratory Medicine 2024; 19: 982
doi: 10.5826/mrm.2024.982