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REVIEW

Idiopathic Pulmonary Fibrosis: 8 Years On After Nintedanib and Pirfenidone Approval—What Is on the Horizon?

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Abstract

Purpose of Review The approval of nintedanib and pirfenidone has changed the treatment landscape of idiopathic pulmonary fibrosis (IPF); however, both drugs only slow disease progression and are burdened by tolerability issues. We summarize the most advanced developmental drugs in IPF, but also mention selected compounds in earlier phases.

Recent Findings Several compounds are currently being tested in IPF; the number of trials has increased exponentially in the last 3 years. Four compounds have reached phase 3: BI101550, an oral PDE4B preferential inhibitor; Pamrevlumab, an anticonnective tissue growth factor intravenous monoclonal antibody; Pentraxin-2, a recombinant human form of serum amyloid protein; Treprostinil, a synthetic prostanoid, with an inhaled formulation, currently used for pulmonary hypertension.

Summary New drugs are likely to reach the clinic in the near future. This will provide more opportunities for treatment of IPF but will also pose unprecedented challenges regarding drug selection and administration(i.e., sequential vs. combination).

Keywords Idiopathic pulmonary fibrosis · Treatment · BI1015550 · Pamrevlumab · Pentraxin-2 · Treprostinil

Introduction

Idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias, is a chronic, progressive, and ultimately fatal disease characterized radiologically and histologically by the usual interstitial pneumonia (UIP) pattern of fibrosis [1–3]. Although disease pathogenesis remains incompletely understood, IPF is believed to result from and exuberant and dysregulated reparative response following recurrent alveolar epithelial cell (AEC) injury [4]. Aberrantly activated AECs secrete a multitude of cytokines and chemokines, which induce fibroblast recruitment, activation, proliferation, and differentiation to myofibroblasts [5]. Several factors have been associated with the development and progression of IPF, including, among others, smoking, chronic microaspiration of gastric content, occupational/environmental exposure, pollution, and subclinical viral infection [6–9]. These triggers are likely to interact with host genetic factors, including, among others, rare variants within telomerase-related genes [10] or *MUC5B* rs35705950 promoter polymorphism [11], to determine the disease. Innate and acquired immunity [12], epigenetic changes [13], telomere attrition [14], mitochondrial dysfunction [15], and cellular senescence [16] are additional likely contributors to disease pathogenesis.

Historically, IPF has been treated with a combination of corticosteroids and immunosuppressants (with or without N-acetylcysteine), the rationale being that chronic inflammation was considered a prerequisite for the disease to develop [17]. However, this treatment strategy has been proven not only inefficacious but also harmful [18]. Therefore, a multitude of potential treatments has been tested in randomized controlled trials (RCTs) in an effort to find a real cure for IPF; yet, most of these trials have yielded negative results (Table 1). Currently, two drugs are approved worldwide for the treatment of IPF: pirfenidone and nintedanib [19]. Pirfenidone acts by downregulating

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Table 1 Phase III clinical trials conducted in IPF

	Compound	Primary outcome	Patients enrolled (*n*)	Outcome	NCT numbers
ACE-IPF	*Warfarin*	*Time to death, hospitalization, or FVC decline ≥ 10%*	*145*	Prematurely discontinued	*NCT00957242*
ARTEMIS-IPF	*Ambrisentan*	*Time to IPF progression (death, respiratory hospitalization, or FVC and DLco decrease)*	*494*	Prematurely discontinued	*NCT00768300*
ASCEND	*Pirfenidone*	*Change in FVC%*	*555*	Primary endpoint met	*NCT01366209*
BUILD 1-3	*Bosentan*	*Exercise capacity, time to IPF progression (decrease in FVC ≥ 10%, DLco ≥ 15%, or acute exacerbation) or death*	*158 + 616*	Primary endpoint not met	*NCT00391443 NCT00071461*
CAPACITY 1-2	*Pirfenidone*	*Change in FVC*	*344 + 435*	Primary endpoint met	*NCT00287716 NCT00287729*
CleanUp-IPF	*Co-trimoxazole or doxycycline*	*Time to first nonelective respiratory hospitalization or death*	*513*	Prematurely discontinued	*NCT02759120*
INPULSIS 1-2	*Nintedanib*	*Change in FVC*	*515 + 551*	Primary endpoint met	*NCT01335464 NCT01335477*
INSPIRE	*Interferon gamma*	*Overall survival time*	*826*	Prematurely discontinued	*NCT00075998*
INSTAGE	*Sildenafil + nintedanib*	*Change in SGRQ*	*274*	Prematurely discontinued	*NCT02802345*
ISABELA 1-2	*Ziritaxestat*	*Rate of decline of FVC*	*525 + 781*	Prematurely discontinued	*NCT03711162 NCT03733444*
PANTHER	*Prednisone, azathioprine, N-acetylcysteine*	*Change in FVC*	*264*	Prematurely discontinued	*NCT00650091*
STEP-IPF	*Sildenafil*	*Improvement of at least 20% in the 6MWT distance*	*180*	Prematurely discontinued	*NCT00517933*

6MWT six-minute walking test, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *SGRQ* Saint George Respiratory Questionnaire

transforming growth factor (TGF)-β, one of the most potent profibrotic cytokines, and tumor necrosis factor (TNF)-α, both in vitro and in vivo [20–22], although its mechanism of action is known only partially. Nintedanib is an intracellular tyrosine kinase inhibitor, which, by acting on fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), interferes with the signaling needed for the proliferation and migration of fibroblasts and their differentiation to myofibroblasts [23–25]. Apart from the respective pivotal studies [26, 27], the efficacy of both nintedanib and pirfenidone in reducing functional decline, as assessed by annual change in forced vital capacity (FVC) and disease progression, has been confirmed by real word and registry data [28–34]. However, both drugs have tolerability issues, mainly skin rash and gastrointestinal discomfort with pirfenidone and diarrhea with nintedanib [25, 35], which lead to drug discontinuation in a significant minority of patients [36–38]. Thus, the unmet IPF need remains high, and more efficacious and better tolerated drugs are urgently needed. In this review, we summarize and critically discuss the most advanced developmental drugs in IPF, with the aim to provide the reader with a glimpse of what the landscape of IPF treatment looks like. However, selected compounds in earlier phases of development are also mentioned (Table 2).

BI1015550

BI1015550 is an oral phosphodiesterase (PDE) 4B preferential inhibitor [39•]. PDEs are a superfamily of enzymes composed of more than 100 isoforms. They act by hydrolyzing cyclic nucleotides, in particular cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP), thus regulating their intracellular concentration [40]. The PDE4 A-D family displays high specificity for cAMP but no activity on cGMP [41]. Therefore, PDE4 exerts proinflammatory activities by blocking the cAMP pathways mediated by both protein kinase A (PKA) and exchange factors activated by cAMP (Epac1/2) [42]. PKA reduces the production of proinflammatory cytokines via phosphorylation of cAMP-responsive element-binding

Table 2 Ongoing phase 2 clinical trials in IPF

Compound	Molecular profile	Primary endpoint	Patients to enroll	Status	Estimated completion date	Concomitant antifibrotic therapy	NCT number
AK3280	*Oral pirfenidone analog*	*Change in absolute FVC from baseline through week 24*	*105*	*Not yet recruiting*	*October 2024*	*Not allowed*	*NCT05424887*
ARO-MMP7	*Inhaled RNA interference molecule targeting MMP7*	*Number of AE occurring through day 85*	*77*	*Recruiting*	*August 2024*	*Not allowed*	*NCT05537025*
Autologous stem cells	*Bronchoscopy instilled autologous bronchial stem cells*	*Change in absolute FVC from baseline through week 48*	*20*	*Recruiting*	*October 2023*	*NA*	*NCT02745184*
BBT-877	*Oral autotaxin and lysophosphatidic acid inhibitor*	*Change in absolute FVC from baseline through week 24*	*120*	*Recruiting*	*December 2024*	*Allowed*	*NCT05483907*
C21	*Oral angiotensin II type 2 receptor agonist*	*Number of AE occurring through week 36*	*60*	*Recruiting*	*December 2023*	*Not allowed*	*NCT04533022*
CSL312 garadacimab	*Monoclonal antibody targeting activated factor XII*	*Number of AE occurring through week 14, presence of antidrug antibodies*	*80*	*Recruiting*	*July 2023*	*Not allowed*	*NCT05130970*
Cudetaxestat	*Oral autotaxin inhibitor*	*Change in absolute FVC from baseline through week 26*	*200*	*Not yet recruiting*	*March 2024*	*Allowed*	*NCT05373914*
DWN12088	*Oral prolyl-tRNA synthetase inhibitor*	*Change in absolute FVC and number of AE from baseline through week 24*	*102*	*Recruiting*	*August 2024*	*Allowed*	*NCT05389215*
ENV-101 taladegib	*Oral small molecule inhibiting Hedgehog pathway*	*Number of AE, change in vital signs, and number of hospitalizations occurring through week 12*	*60*	*Recruiting*	*August 2023*	*Not allowed*	*NCT04968574*
GKT137831	*Oral inhibitor of NADPH oxidase isoforms*	*Change in surrogate biomarker of oxidative stress through week 24*	*60*	*Recruiting*	*April 2023*	*NA*	*NCT03865927*
HEC585	*Second-generation pirfenidone analog*	*Change in FVC% predicted from baseline through week 24*	*270*	*Recruiting*	*May 2023*	*Not allowed*	*NCT05060822*
HZN-825	*Oral lysophosphatidic acid 1 receptor antagonist*	*Change in FVC% predicted from baseline through week 24*	*360*	*Recruiting*	*July 2025*	*Allowed*	*NCT05032066*
Ifetroban	*Oral thromboxane receptor antagonist*	*Change in absolute FVC from baseline through month 12*	*200*	*Not yet recruiting*	*April 2027*	*Allowed*	*NCT05571059*
Jaktinib	*Oral Janus kinase 1–3 inhibitor*	*Change in absolute FVC from baseline through week 24*	*90*	*Active, not recruiting*	*December 2023*	*Not allowed*	*NCT04312594*

Table 2 (continued)

Compound	Molecular profile	Primary endpoint	Patients to enroll	Status	Estimated completion date	Concomitant antifibrotic therapy	NCT number
LTP001	*NA*	*Change in FVC% predicted from baseline through week 26*	*94*	*Recruiting*	*February 2025*	*Allowed*	*NCT05497284*
LYT-100 deupirfenidone	*Oral deuterated form of pirfenidone*	*Change in absolute FVC from baseline through week 26*	*240*	*Recruiting*	*March 2024*	*Not allowed*	*NCT05321420*
PLN-74809	*Oral αvβ6 and αvβ1 integrin inhibitor*	*Number of AE occurring through week 24*	*120*	*Active, not recruiting*	*March 2023*	*Allowed*	*NCT04396756*
PLN-74809	*Oral αvβ6 and αvβ1 integrin inhibitor*	*Change in collagen I deposition through week 12*	*12*	*Recruiting*	*October 2023*	*Allowed*	*NCT05621252*
REGEND001	*Autologous bronchial stem cells*	*Number of AE occurring through week 24*	*24*	*Recruiting*	*September 2024*	*Not allowed*	*NCT05657184*
RXC007	*Oral ROCK2 inhibitor*	*Number of AE occurring through week 12*	*64*	*Recruiting*	*April 2024*	*Allowed*	*NCT05570058*
Saracatinib	*Oral SRC kinase family inhibitor*	*Change in absolute FVC and number of AE from baseline through week 24, pharmacodynamics*	*49*	*Recruiting*	*June 2024*	*Not allowed*	*NCT04598919*
SHR-1906	*Intravenous anti-CTGF monoclonal antibody*	*Change in FVC% predicted from baseline through week 24*	*108*	*Not yet recruiting*	*May 2024*	*Allowed*	*NCT05722964*
TTI-101	*Oral STAT3 inhibitor*	*Number of AE occurring through week 12*	*100*	*Recruiting*	*March 2025*	*Only nintedanib allowed*	*NCT05671835*
ZSP1603	*Oral VEGFR2, FGFRs, and PDGFRβ inhibitor*	*Number of AE occurring through week 16, pharmacokinetic*	*36*	*Recruiting*	*October 2022*	*Not allowed*	*NCT05119972*

AE adverse events, *CTGF* connective tissue growth factor, *FGFR* fibroblast growth factor receptor, *FVC* forced vital capacity, *MMP7* matrix metalloproteinase-7, *NA* not available, *NADPH* nicotinamide adenine dinucleotide phosphate, *PDGFR* platelet-derived growth factor receptor, *RNA* ribonucleic acid, *ROCK2* Rho-associated coiled-coil containing protein kinase 2, *SMURF1* SMAD-specific E3 ubiquitin protein ligase 1, *STAT3* signal transducer and activator of transcription 3, *VEGFR2* vascular endothelial growth factor receptor 2

protein (CREB), through the modulation of the transcriptional activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and by interfering with B cell lymphoma 6 protein (Bcl-6) [43–46]. Epac1/2, on the other hand, shows anti-inflammatory activities through epigenetic modulation of NFkB targets [47]. Owing to their well-established anti-inflammatory properties, PDE4 inhibitors are approved for the treatment of inflammatory airway disease, psoriatic arthritis, and atopic dermatitis [41].

PDE4 inhibition has also antifibrotic effects. In bleomycin-treated mice and rats, roflumilast reduced the transcription and bronchoalveolar lavage (BAL) levels of several profibrotic genes, including TNFα and TGF-β, and improved fibrotic changes in the lung [48]. The antifibrotic effect of PDE4 inhibitors has also been shown in other animal models of fibrosis, such as type II AEC injury [49] and graft-vs-host disease [50], and with other compounds, such as cilomilast [51]. In vitro, human lung fibroblasts exposed to PDE4 inhibitors show lower expression of profibrotic proteins (or their mRNA), such as connective tissue growth factor (CTGF), collagen-α1, fibronectin, or α-smooth muscle actin, which are markers of fibrosis, fibroblast proliferation, or fibroblast-to-myofibroblast differentiation [52–55].

Preclinical studies have confirmed the anti-inflammatory properties of BI1015550 through reduction of TNF-α and interleukin 2 (IL-2) production by mononuclear blood cells and inhibition of monocyte and neutrophil influx in the lung. The compound was also efficacious in two different animal models of fibrosis, with improvement of FVC values in the bleomycin model and reduced BALF inflammation in the silica model in mice. Furthermore, BI1015550 reduced TGF-β-induced collagen production in human fibroblasts, alone or synergistically with nintedanib [39•].

The safety and efficacy of BI1015550 have been evaluated in a phase 2 trial in IPF; 147 patients were randomized to either BI1015550 or placebo with a 2:1 ratio and stratified based on background treatment (nintedanib or pirfenidone) [56••]. Inclusion criteria included a high-resolution CT pattern of definite or probable UIP, as assessed centrally, FVC ≥ 45%, and DLco between 25 and 80% of the predicted value. BI1015550 was administered orally at a dose of 18 mg twice a day for 12 weeks. Notably, the authors used a Bayesian approach to reduce the number of patients randomized to placebo, including historical data from patients included in the placebo arms of previous nintedanib trials [57]. The study met its primary endpoint irrespective of background antifibrotic therapy. Indeed, the median change in FVC was 5.7 ml in the BI1015550 group and − 81.7 ml in the placebo group among patients without background antifibrotic therapy and 2.7 ml in the BI1015550 group and − 59.2 ml in the placebo group among patients with background antifibrotic use. No differences in the secondary endpoints of change in diffusing capacity of the lung for carbon monoxide (DLco) or change in quality of life were found. The most frequently reported adverse events were gastrointestinal, in particular diarrhea, but the proportion of patients with serious or severe adverse events was similar in the two trial groups.

A phase 3 RCT (NCT05321069), FIBRONEER-IPF, is ongoing. This study will enroll 963 patients with IPF. Inclusion criteria include an FVC ≥ 45% and DLco between 25 and 90% of the predicted value. Patients will be randomized to two doses of BI1015550 or placebo for 52 weeks. Estimated study completion date is November 2024. The primary endpoint is the change in absolute FVC; secondary endpoints include time to functional worsening (decline in FVC ≥ 10% or DLco ≥ 15%), time to the first occurrence of the composite outcome comprehending hospitalization for respiratory cause, death or acute exacerbation, time to acute exacerbation, time to hospitalization for respiratory cause or death, absolute change in FVC% and DLco% predicted, and change in Living with Pulmonary Fibrosis Questionnaire score.

Pamrevlumab

Pamrevlumab, formerly known by its developmental name FG-3019, is a fully human recombinant antibody that binds to CTGF, inhibiting it from binding to its receptors [58•].

CTGF is a secreted glycoprotein that interacts with a plethora of cytokines involved in connective tissue regeneration and wound healing [59, 60]. CTGF has a key role in fibroblast proliferation and differentiation to myofibroblasts. Treatment of fibroblasts with recombinant CTGF and TGF-β increases profibrotic markers in fibroblasts, thus suggesting a synergistic effect of CTGF and TGF-β in inducing pulmonary fibrosis [61]. A similar positive feedback loop has been observed between CTGF and other fibrogenic molecules such as VEGF and integrins [62]. Moreover, CTGF appears to act as TGF-β cofactor: in fact, in CTGF knockout mice, TGF-β cannot exert its profibrotic activity [63, 64]. In IPF lung, CTGF is increased both transcriptionally and translationally in AECs and fibroblasts [65, 66].

In vivo, Pamrevlumab reduces collagen deposition and fibrosis in different animal models, including bleomycin- and radiotherapy-induced lung fibrosis [64, 67]. Pamrevlumab is able to induce fibroblast apoptosis in a model of mesothelioma [68], and a similar effect is also plausible on IPF myofibroblasts [69].

Pamrevlumab has been evaluated in two phase 2 studies in IPF. The first was an open-label study that assessed the safety and efficacy of two different doses of the drug (15 or 30 mg/kg) [70]. Patients received Pamrevlumab intravenously every 3 weeks for 45 weeks. FG-3019 displayed a good safety and tolerability profile. Notably, changes in fibrosis correlated with changes in pulmonary function,

and FG-3019 was associated with an increase in FVC and reduction in the extent of fibrosis in about one-third of patients. The PRAISE trial randomized 103 IPF patients to Pamrevlumab 30 mg/kg or placebo over 48 weeks [71••]. Inclusion criteria included a definite UIP pattern on chest CT or a probable UIP and lung biopsy, an FVC ≥ 55%, and a DLco ≥ 30%; background antifibrotic treatment was not allowed. The study met its primary endpoint. Indeed, Pamrevlumab reduced the decline in FVC% predicted by 60% at week 48 (mean change from baseline − 2.9% with Pamrevlumab vs − 7.2% with placebo; $p = 0.033$). The secondary endpoints of absolute decline in FVC, number of patients with an FVC decline ≥ 10%, and extent of lung fibrosis on HRCT were also met. Conversely, no differences in quality of life as assessed by the Saint George Respiratory Questionnaire were observed. The safety and tolerability profile of Pamrevlumab were similar to those of placebo.

The phase 3 Zephyrus I and II trials (NCT03955146-NCT04419558) are currently ongoing. Each study will enroll 340 IPF patients. Inclusion criteria include age between 40 and 80 years, FVC percentage of predict between 45 and 90%, DLco between 25 and 90%, and fibrotic changes at HRCT between 10 and 50%. Background antifibrotic therapy is not allowed. Patients will be randomized to Pamrevlumab 30 mg/kg or placebo administered intravenously every 3 weeks for 48 weeks. Estimated completion date is June 2024 for Zephyrus I and May 2023 for Zephyrus II. For both studies, the primary endpoint is the change in FVC from baseline; secondary endpoints include time to disease progression (decline in FVC ≥ 10% or death), time to respiratory hospitalization, death and acute exacerbation, as single occurrence or as composite outcome, and changes in the quantitative lung fibrosis score.

Pentraxin-2

Pentraxin-2, also known as serum amyloid protein (SAP), is a pleiotropic pentameric protein secreted by the liver. SAP is a highly conserved protein, and neither genetic deficiencies nor polymorphisms have been reported to date [72]. It exerts antifibrotic activities through different mechanisms. Specifically, SAP inhibits monocyte-to-fibroblast differentiation and activation of profibrotic macrophages by inducing IL-10 production. SAP also interferes with numerous profibrotic signals such as thrombin, tryptase, IL-4, and IL-13 [73]. Conversely, inhibition of SAP induces persistent inflammation and fibrosis following bleomycin challenge in mice [74]. Reduced serum levels of SAP, or increased levels with reduced activity through desialylation, have been found in patients with IPF and other fibrotic diseases [75–78]. This effect is likely to be secondary to the accumulation of SAP in fibrotic and injury sites [79].

In a mouse model of kidney fibrosis, SAP reduced inflammation as well as fibroblast and myofibroblast activation [79]. In a mouse model of bleomycin-induced lung fibrosis, the administration of human SAP reduced inflammation and fibrosis through inhibition of TGF-β-induced macrophage activity [76, 80, 81].

Owing to its antifibrotic properties, a recombinant form of human Pentraxin-2, also known as PRM-151, has been evaluated in IPF [82]. In a phase 2 study (PRM-151–202), 116 IPF patients were randomized in a 2:1 ratio to Pentraxin-2 or placebo over 24 weeks [83]. The drug was administered intravenously at a dose of 10 mg/kg every 4 weeks with a loading regimen of three doses at the start of treatment (day 1, 3, and 5). Inclusion criteria were a definite/probable UIP pattern on chest CT, an FVC between 50 and 90%, and DLco between 25 and 90% of the predicted values; concurrent therapy with pirfenidone or nintedanib was permitted if the dosage was stable for at least 3 months. The study met its primary endpoint of mean change in FVC% predicted from baseline to week 28, which was − 2.5% in patients treated with recombinant human Pentraxin-2 and − 4.8% in those in the placebo group. In addition, the change in 6-min walk distance was − 0.5 m for patients treated with Pentraxin-2 vs. − 31.8 m for those in the placebo group ($p < 0.001$). Conversely, no difference was found in quantitative parenchymal features on HRCT or changes in DLco. The drug was safe and well tolerated with the most common adverse events in the Pentraxin-2 vs. placebo group being cough (18% vs. 5%, respectively) and fatigue (17% vs. 10%, respectively).

Patients who completed the 28-week double-blind period of the PRM-151–202 trial were eligible to participate in the open-label extension study (at 76 and 128 weeks) [84, 85]. Specifically, patients previously enrolled in the Pentraxin-2 arm continued this treatment while those previously randomized to placebo crossed over to Pentraxin-2. Both analyses confirmed that long-term treatment with Pentraxin-2 was well tolerated and that the positive effects on FVC and 6-min walking distance were persistent on continuation and positive in patients who crossed over from placebo.

A phase 3 trial (NCT04594707), STARSCAPE, was conducted to confirm the efficacy and safety of recombinant human Pentraxin-2 in patients with IPF. The study has recently been terminated for futility with the results yet to be released. This study enrolled 665 patients. Inclusion criteria were an FVC ≥ 45% and DLco between 30 and 90% of the predicted values. The primary endpoint was the change in absolute FVC while secondary endpoints included changes in 6MWT, FVC% and DLco, time to respiratory-related hospitalization, acute exacerbation, or all-cause mortality over 48 weeks. Quality of life, as assessed by SGRQ and University of California, San Diego-Shortness of Breath Questionnaire, was also evaluated.

Treprostinil

Treprostinil is a chemically stable prostacyclin analog, developed and approved for the treatment of pulmonary hypertension (PH) [86]. This compound acts through a complex network of prostanoid receptors on different cellular types [87]. In particular, prostaglandin I2 receptor (IP), prostaglandin D2 receptor 1 (DP_1), and prostaglandin E2 receptor 2 (EP_2), all G_s protein-coupled receptors, increase cellular concentrations of cAMP [88]. In turn, the increase in cAMP inhibits the extracellular regulated kinase (Erk1/2) signaling, thus blocking several profibrotic pathways [89]. Potential antifibrotic effects of Treprostinil include reduction of TGF-β- and PDGF-induced collagen deposition [90], inhibition of fibroblast proliferation through nuclear accumulation of cAMP [91], and modulation of inflammatory cell accumulation via inhibition of NFkB, as shown in bleomycin-induced pulmonary fibrosis in mice [92]. Another signaling pathway inhibited by increased cAMP levels is the Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ). These nuclear factors have a role in the transcription of TGF-β-activated genes [93]. Additional antifibrotic activities may be due to the immunomodulatory effects of prostanoid receptors [94–96].

Treprostinil was initially evaluated as a continuous subcutaneous infusion to treat group 1 PH [97]. To avoid infusion-related side effects, an inhaled formulation has been developed, and this has led to the approval of Treprostinil for the treatment of PH in USA, Israel, and Argentina [98]. Further studies have suggested the efficacy of inhaled Treprostinil in group 3 PH, including PH secondary to IPF [99, 100]. The INCREASE trial, a phase 3 RCT, assessed the safety and efficacy of inhaled Treprostinil in patients with PH secondary to ILD [101]. In this trial, patients had PH confirmed by right heart catheter and ILD confirmed by centrally reviewed CT scans and were allowed to remain on a stable dose of antifibrotic therapy. The drug was administered by an ultrasonic, pulsed-delivery nebulizer at a dose of 6 µg per breath, starting with 3 breaths 4 times a day, with the dose increased by 1 breath every 3 days until reaching the target dose of 9 breaths per session, up to a maximum of 12 per session. The study met its primary endpoint of change in peak 6-MWD from baseline through week 16. Change in NTproBNP levels and time to clinical worsening were also significantly different favoring Treprostinil. The study drug was well tolerated, and the most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Notably, 22% of patients in the Treprostinil arm and 39% of patients in the placebo arm experienced exacerbation of their underlying disease, a percentage substantially higher than in other clinical trials of IPF/fibrotic ILD [27, 102•]. A post hoc analysis of this study looked at patients with IPF and found that Treprostinil treatment was associated with preserved lung function, as assessed by FVC, and reduced risk of acute exacerbation [102•].

Based on these results, two parallel RCTs (TETON) will evaluate the efficacy of inhaled Treprostinil, either alone or on background antifibrotic therapy, in patients with IPF (NCT05255991; NCT04708782) [103••]. Each study will enroll 396 patients. Inclusion criteria include an FVC ≥ 45% predicted. Pirfenidone and nintedanib are allowed provided patients are on a stable and optimized dose for ≥ 30 days

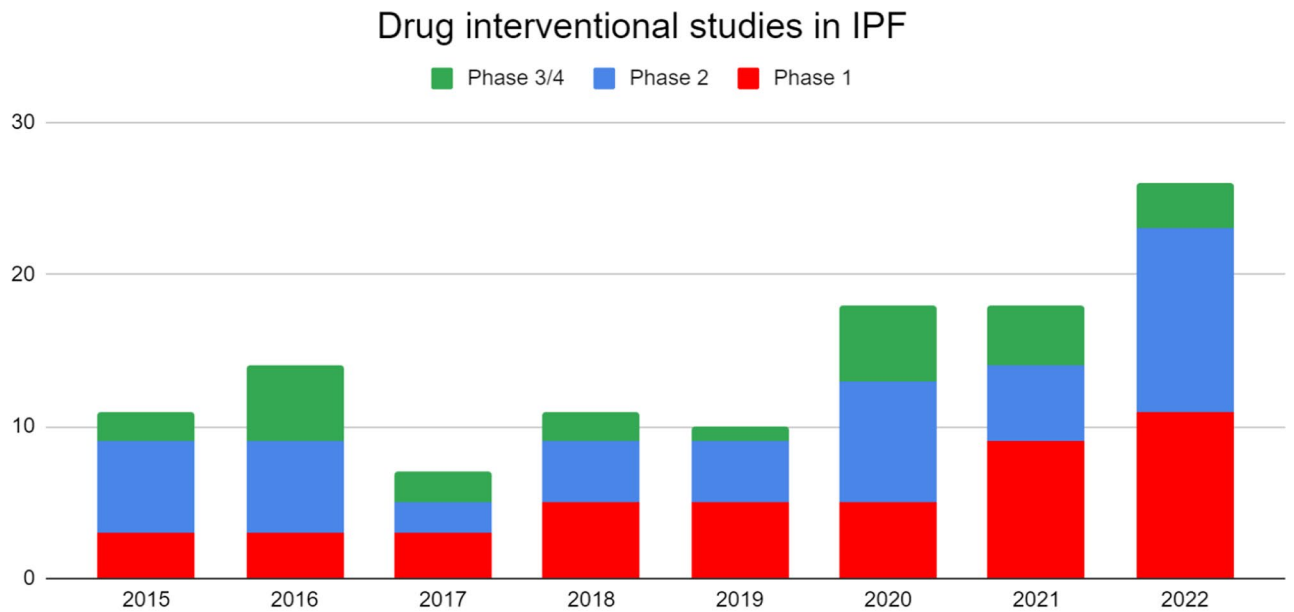

Fig. 1 Number of clinical trials in idiopathic pulmonary fibrosis since the approval of pirfenidone and nintedanib, stratified by clinical phase

prior to baseline. Treprostinil will be administered as in the INCREASE study [101], and the study is expected to be concluded in June 2025. The primary endpoint is the change in absolute FVC from baseline to week 52; secondary endpoints include time to clinical worsening and acute exacerbation, overall survival, FVC% decline, and change in King's Brief Interstitial Lung Disease Questionnaire score.

Future Perspectives

One decade after the approval of pirfenidone and nintedanib, the unmet need in IPF remains high. A large number of trials have been conducted, particularly in the last 3 years (Fig. 1; Table 2). Intravenous or endobronchial delivery of mesenchymal stem cells has proven safe and potentially efficacious, but the available data does not allow drawing firm conclusions; a number of phase 1 and phase 2 studies are ongoing [104••]. TRK-250 is an inhaled small interfering RNA with the potential to suppress TGF-β expression. A phase 1 study has recently been completed, but the results have not been released yet [105]. C21, an oral angiotensin II type 2 receptor agonist, has been associated with improvement of FVC in an *interim* analysis of an ongoing Phase 2 trial in IPF [106]. Dasatinib + quercetin are oral senolytics that act through inhibition of antiapoptotic pathways. In a recently completed phase 1 study, these drugs were safe and well tolerated [107].

Finally, two studies [108, 109] have shown that the combination of nintedanib and pirfenidone is safe and well tolerated; a phase 4 study is currently evaluating the safety and efficacy of the combination pirfenidone and nintedanib compared to a "switch monotherapy" (i.e., switching from the current to the other of the two drugs prescribed as monotherapy) in patients with IPF experiencing progression despite antifibrotic therapy (NCT03939520).

Conclusions

The approval of nintedanib and pirfenidone has changed the landscape of IPF treatment, and more drugs are likely to reach the clinic in the next few years. This represents an unprecedented opportunity; yet, it also poses new challenges regarding the choice of the drug and the possibility to combine them or to use them sequentially. However, the development of truly efficacious drugs able to halt or even reverse fibrosis requires a better understanding of the mechanisms involved in disease pathogenesis with the final aim to provide the right patient with the right drug at the right time.

Compliance with Ethical Standards

Conflict of Interest PS reports institutional grants, personal fees, and non-financial support from PPM Services and Boehringer Ingelheim; institutional grants from Roche; personal fees from Chiesi, Novartis, Galapagos, Lupin, Pieris, Behring, AstraZeneca, Glycocore Pharma, and Menarini outside the submitted work; wife employee of AstraZeneca. EB reports personal fees from Boehringer Ingelheim and Roche outside the submitted work. EC reports personal fees from Boehringer Ingelheim outside the submitted work. GC and NB do not have any conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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