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REVIEW

Treatment of idiopathic pulmonary fibrosis: an update on emerging drugs in phase II & III clinical trials

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ABSTRACT

Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive, debilitating lung disease with poor prognosis. Although two antifibrotics have been approved in the past decade there are no curative therapies.
Areas covered: This review highlights the current landscape of IPF research in the development of novel compounds for the treatment of IPF while also evaluating repurposed medications and their role in the management of IPF. The literature search includes studies found on PubMed, conference abstracts, and press releases until March 2024.
Expert opinion: Disease progression in IPF is driven by a dysregulated cycle of microinjury, aberrant wound healing, and propagating fibrosis. Current drug development focuses on attenuating fibrotic responses via multiple pathways. Phosphodiesterase 4 inhibitors (PDE4i), lysophosphatidic acid (LPA) antagonists, dual-selective inhibitor of αvβ6 and αvβ1 integrins, and the prostacyclin agonist Treprostinil have had supportive phase II clinical trial results in slowing decline in forced vital capacity (FVC) in IPF. Barriers to drug development specific to IPF include the lack of a rodent model that mimics IPF pathology, the nascent understanding of the role of genetics affecting development of IPF and response to treatment, and the lack of a validated biomarker to monitor therapeutic response in patients with IPF. Successful treatment of IPF will likely include a multi-targeted approach anchored in precision medicine.

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1. Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease (ILD) with a poor prognosis and survival of 2–4 years post diagnosis [1–3]. Risk factors for IPF include older age, male gender, smoking history, environmental particulate exposure history, and family history. There is a significant burden of disease on health-related quality of life (HRQoL) through dyspnea, chronic cough, hypoxemia, exercise limitation, and loss of autonomy. Furthermore, patients are prone to acute exacerbations which have a high mortality and a median survival time of only 1–4 months [4]. Additional co-morbidities include World Health Organization (WHO) group 3 pulmonary hypertension, coronary artery disease, sleep disordered breathing, depression, and lung cancer adding to overall morbidity and mortality with limited options for treatment [5–7]. The prevalence of IPF has been rising over the past two decades with North American rates of 2.4–2.89 per 10,000 persons and the world's highest prevalent rates in South Korea of 4.5 per 10,000 persons [8]. In addition to the HRQoL impact, care for IPF patients is complex and is associated with significant healthcare-related costs. In Canada and the U.S.A. care of patients with IPF costs 2.5–3.5 times more than for patients without the disease [9]. There is urgent need to develop more effective treatment for patients with IPF as the only current curative therapy is lung transplant which is a high cost procedure with significant lifelong medical care requirements and limited survival [10]. From a geographic perspective lung transplant is a restricted and limited resource further highlighting the global importance of promoting IPF drug development. The pathogenesis of IPF is incompletely characterized but the driving hypothesis is one of recurrent and cumulative microinjury of the alveolar epithelium in a person who is genetically predisposed to anomalous wound healing leading to profibrotic cytokine release, dysregulated fibroblast and myofibroblast response, and increased extracellular matrix accumulation resulting in architectural distortion and lung fibrosis [11]. Immense research has contributed to standardized diagnostics and classification of patients with IPF, a better understanding of epidemiologic risk factors, genetics, and pathophysiology with multiple trials underscoring the zenith of these efforts. Unfortunately, there are only two approved antifibrotic medications for treatment of IPF both of which slow the rate of decline but do not reverse the disease [12]. The frequency of negative phase III drug trials for IPF is likely driven by a combination of the complexity of the fibrotic signaling pathway without clear understanding of hierarchy of importance in disease progression, lack of validated biomarkers to assess response to treatment, as well as variable rates of progression among patients [13]. At present there are a plethora of novel molecules under investigation for treatment of IPF with a focus on regulating the aberrant fibrogenesis via multiple different pathways (Figure 1). The purpose of this review is to describe current drug

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Article highlights

- LPAR antagonists and integrin αVβ1αVβ6 blockers are novel molecules targeting IPF.
- PDE4B inhibition reduces fibrogenesis while limiting PDE4 inhibitor related side effects.
- Repurposing drugs such as Treprostinil to treat IPF expedites clinical trials.
- IPF therapeutics will benefit from precision medicine focusing on biomarkers and genetics.

development targeting IPF with a focus on completed phase II and active phase III clinical trials.

2. Medical need

Similar to palliative chemotherapy in metastatic malignancy, current anti-fibrotic therapy does not halt the progression of fibrosis and for some patients the side effect profile further reduces quality of life. At present clinical studies are trying to slow down or stop the continued fibrogenesis of IPF; a particular emphasis of these trials needs to be tolerability of a medication patients will likely need for the remainder of their life. To date, there are no approved drug therapies targeting reversal of fibrosis and this is a critical area of need going forward. With the emergence of guidelines for interstitial lung abnormality there also needs to be clarification around the use of anti-fibrotic medications to inhibit development of ILD as there may be a role for preventive therapy. Beyond attenuating progressive fibrosis, additional domains requiring study include drugs that prevent or treat acute exacerbations of IPF. From a symptom perspective we have few tools at our disposal for pharmacologic management of dyspnea and cough. IPF-related cough occurs in up to 80% of patients and is a debilitating symptom that correlates with disease progression while IPF-related dyspnea is a primary driver of decreased health-related quality of life. There are many areas of medical need in the treatment of IPF.

3. Existing treatment

The two current treatments for IPF both fall into the category of anti-fibrotics albeit with very different mechanisms. They are consistently effective across multiple fibrotic subtypes and are an important pillar of IPF management in reducing the rate of FVC decline; unfortunately each medication has a significant side effect profile that can impact patient quality of life or lead to drug discontinuation.

3.1. Pirfenidone

Pirfenidone is an anti-fibrotic medication with concurrent anti-inflammatory properties that has multiple proposed pleiotropic mechanisms of action. TGF-β induction drives fibroblast proliferation, myofibroblast transdifferentiation, collagen formation, and extracellular matrix deposition [14]. In vitro and

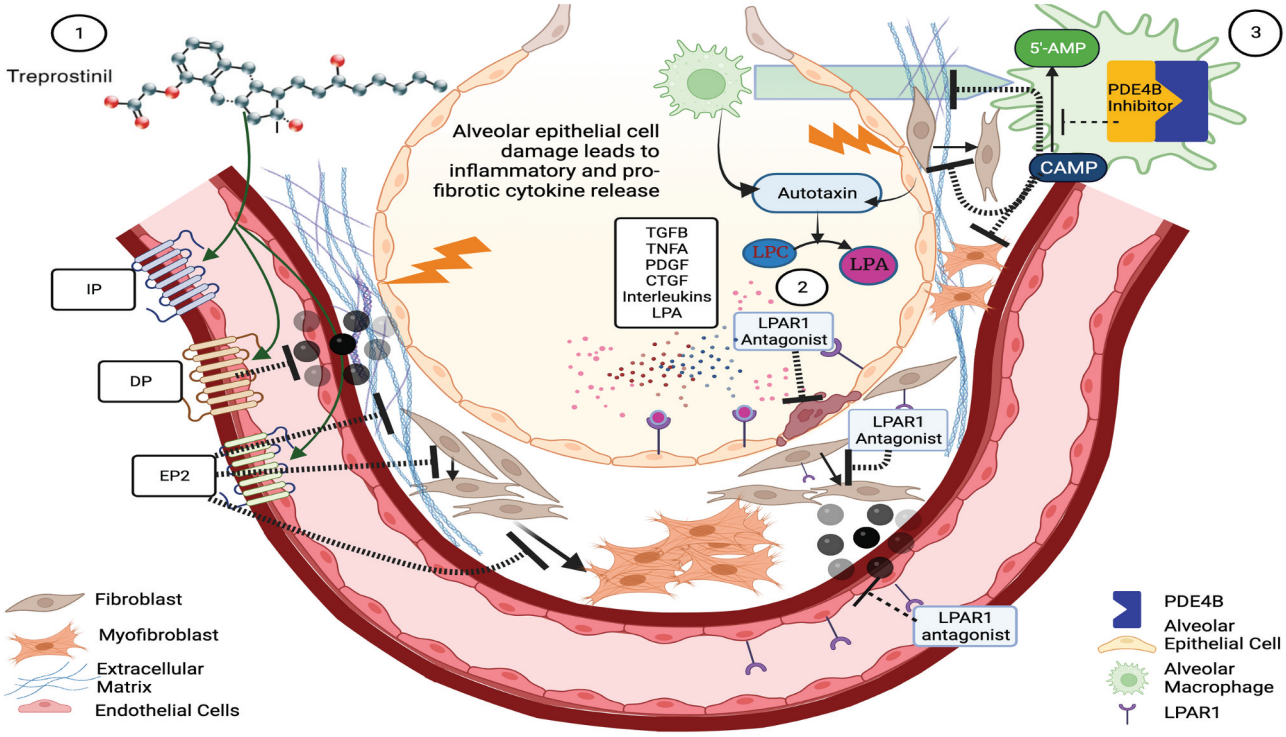

Figure 1. Demonstrates proposed anti-fibrotic mechanisms of Treprostinil, LPAR1 antagonists, and PDE4B inhibitors. 1) Treprostinil exerts anti-fibrotic action via inhibition of fibroblast migration and proliferation, inhibition of fibroblast to myofibroblast transition, inhibition of pro-fibrotic cytokine release via reduced vascular leak, and reduction in extracellular matrix deposition. 2) LPAR1 antagonists have a proposed anti-fibrotic mechanism that includes reduction in epithelial apoptosis, inhibition of fibroblast migration and proliferation, and decreased vascular leak reducing pro-fibrotic cytokine release. 3) PDE4B inhibitor's hypothetical anti-fibrotic effect is mediated by blocking degradation of CAMP resulting in reduced extracellular matrix deposition, fibroblast proliferation, and myofibroblast differentiation. Figure created with BioRender.com.

in vivo analysis has demonstrated that pirfenidone attenuates downstream production of multiple TGF-β induced mediators and proteins including α-smooth muscle actin (SMA), collagen type I-III, fibronectin, p38, and SMAD3 [15]. Recent transcriptomic and immunohistochemical analysis of IPF lung tissue suggests a hyperactivation of of myocardin-related transcription factor (MRTF) in mesenchymal cells such as fibroblasts and myofibroblasts. MRTF functions as a mechanosensor modulating parenchymal cell response to extracellular matrix stiffness via actin dynamics directing cytoskeletal proliferation and cellular motility. Pirfenidone was noted to alter MRTF signaling via inhibition of MRTFA nuclear translocation in lung fibroblasts cultured from IPF explants at experimentally determined IC_{50} of 50–150 μM which is a clinically achievable concentration of pirfenidone with current standard dosing of pirfenidone [16,17]. Three phase III RCT known as CAPACITY I, CAPACITY II, and ASCEND were performed to evaluate the efficacy and safety of pirfenidone in treatment of IPF at a target dose of 2403 mg/day [18,19]. In pooled assessment of these three trials, 1247 patients were analyzed and those treated with pirfenidone had a 38% improvement in progression free survival and there was a 40.7% relative difference in the rate of FVC decline with placebo treated patients losing a mean of 363 ml/year and pirfenidone treated patients losing 216 ml/year. From a safety perspective there were multiple side effects with the most common being sun sensitive skin rash, nausea, anorexia, and asthenia and 11.9% of patients discontinued pirfenidone due to side effects [20]. Pirfenidone was approved by the FDA in 2014 for treatment of IPF; post-marketing real world analyses show persistent long-term effects of pirfenidone with ongoing reduction in the rate of FVC decline and survival benefit [21–23]. In an attempt to reduce systemic side effects, aerosolized pirfenidone delivered via nebulization allowing for a lower dose of drug administered has been developed. Recent phase 1b data demonstrated a lower incidence of pirfenidone associated side effects with the inhaled compound and large phase II trials for this compound for pulmonary fibrosis are planned [24]. With a similar goal of attenuating systemic side effects, there is a phase IIb trial underway looking at LYT-100, a deuterated form of pirfenidone, with the aim of garnering anti-fibrotic and anti-inflammatory effect by maintaining the same area under the curve (AUC) as pirfenidone but reducing side effects by lowering the peak serum concentration [25].

3.2. Nintedanib

Nintedanib is the second anti-fibrotic medication approved for use in patients with IPF. It is an oral tyrosine kinase inhibitor that operates via inhibition of three major angiogenic signaling pathways: selective inhibition of vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptors (FGFR), and platelet derived growth factor receptors (PFGDR). Analysis was performed in two phase III trials (INPULSIS-1 and INPULSIS-2) evaluating the safety and efficacy of 150 mg po bid Nintedanib for treatment of IPF in 1066 patients randomized in a 3:2 ratio of Nintedanib to placebo [26]. In both INPULSIS-1 and INPULSIS-2 the rate of FVC decline was attenuated with addition of Nintedanib when compared to control (−114.7 ml vs −239.9 ml, and −113.6 ml vs −207.3 ml respectively). There was a significant reduction in time to acute exacerbation of IPF when treated with Nintedanib for patients in INPULSIS-2 but not INPULSIS-1. Based on the results from these trials Nintedanib was approved by the FDA as a first line therapy for IPF in 2014. The most frequent side effect was diarrhea occurring in approximately 60% of patients and necessitating drug discontinuation in less than 5% of patients. Post hoc analysis of INPULSIS confirmed that in patients with IPF and preserved lung volumes (FVC >90%) there was a similar rate of FVC decline as patients with more advanced disease (FVC £90%). Nintedanib was effective in reducing the rate of FVC decline in patients with baseline reduced and normal lung volumes [14,15]. In open label extension and real world analyses the long-term use of Nintedanib has proven to be safe and efficacious with suggestion of improved overall and progression free survival [27–29].

4. Current research goals

At present most of the compounds in phase II or phase III testing remain targeted toward reducing the proliferation of fibrosis once a diagnosis of IPF has been established. The necessary inclusion of standard of care (SOC) anti-fibrotic treatment (Nintedanib or pirfenidone) in both the placebo and treatment arms creates added complexity as it is difficult to predict synergistic effects as well as infer statistical difference given the already attenuated decline in FVC due to SOC antifibrotic therapy. The approach to targeting fibrogenesis ranges from inhibition of specific pathways to molecules with pleiotropic effects.

5. Biological rationale

The development and propagation of fibrosis in the lung is a complex multi-faceted process with ultimate aberrancy in wound healing. There are many pathways of molecular dysfunction that are hypothesis driving in drug development targeting the progression of pulmonary fibrosis. The interstitial microenvironment scaffolding the interplay of communication between injury and repair is an intricate and dynamic network of crosstalk that does not have a single dominant element to target. Given that accumulation of dysregulated fibroblasts and myofibroblasts with accompanying extracellular matrix deposition is the primary mediator of progressive FVC decline it is reasonable to target pathways contributing to fibrogenesis. One of the primary conductors of fibrosis is TGFβ which is a pleiotropic growth factor with extensive downstream fibrogenic effects. Injury and inflammation in the lung result in the increased synthesis of TGFβ and release of latent TGFβ by many cell types including macrophages while epithelial cells can activate latent TGFβ directly via integrin $\alpha_v\beta_6$ [30]. Activation of TGFβ results in fibrosis via a cascade of parallel events including arrested alveolar type II (ATII) growth or transdifferentiation, increased matrix metalloproteinase expression, increased mucous production, persistent microinjury via ATII apoptosis, fibroblast proliferation, myofibroblast differentiation, epithelial to mesenchymal transformation,

smooth muscle cell proliferation, and collagen deposition [31,32]. Connective-tissue growth factor (CTGF) is a secreted protein with anti-fibrotic effect via modulation of the extracellular matrix. Its release is stimulated by pathophysiologic injury as well as by multiple growth factors and cytokines including TGFβ; multiple fibrosing diseases such as radiation fibrosis, hepatic fibrosis, and scleroderma demonstrate upregulated CTGF [33,34]. TGFβ and CTGF work synergistically through a variety of mechanisms including CTGF binding to TGFβ augmenting the pro-fibrotic effects of TGFβ [35]. Blocking TGFβ, CTGF, or integrin $\alpha_v\beta_6$ in rodent models of pulmonary fibrosis inhibits fibrosis [31,36–38].

A mechanism that is relatively new for targeting fibrogenesis but has been used as a means of reducing inflammation is inhibition of phosphodiesterase 4 (PDE4). PDE4 is a specific phosphodiesterase responsible for the degradation of cyclic adenosine monophosphate (cAMP). PDE4 is highly expressed in inflammatory cells including macrophages and monocytes [39]. The ability of PDE4 inhibition to reduce inflammation is multifaceted and related to downstream effects on eosinophils, mast cells, and histamine release and this led to development of a PDE4 inhibitor to target inflammation in COPD (e.g. roflumilast). Apremilast is a PDE4 inhibitor used in the management of psoriasis-related inflammation. These drugs induce significant nausea and vomiting which has limited more widespread use. Careful analysis of the *in vivo* experiments revealed a role for PDE4 inhibition in modulating pulmonary parenchymal architectural distortion with evidence of reduction of subepithelial collagen deposit, prevention of emphysema in rodent models, and minimization of the impact of chronic hypoxia on muscularization of pulmonary arterioles [40]. This led to *in vivo* analysis of PDE4 inhibition via roflumilast administration in a rodent model of pulmonary fibrosis; PDE4 inhibition reduced inflammation associated with the bleomycin model and also reduced the degree of fibrosis, right ventricular hypertrophy, and pulmonary artery thickening [40]. PDE4 inhibition resulted in downregulation of IL-13, TNFα, and TGFβ via suppression of macrophage activation [39]. This provides a novel anti-fibrotic approach targeting microinjury and aberrant repair.

Another target for inhibition of fibrogenesis is lysophosphatidic acid (LPA). LPA activates a family of G protein-coupled receptors LPA_{1-6}. In bleomycin models of pulmonary fibrosis LPA levels were increased in bronchoalveolar lavage fluid while LPA_1 knockout mice and an oral LPA_1 receptor antagonist had reduced fibrosis post bleomycin [41,42]. Furthermore, LPA levels were increased in the BAL fluid of patients with IPF while fibroblasts from the BAL had very high levels of LPA_1 expression [41]. In depth analysis revealed multiple domains in which LPA, via LPA_1 signaling, impacts aberrant wound healing and fibrosis; this includes promoting fibroblast migration and apopotic resistance, increasing pulmonary vascular leak, and alveolar epithelial cell apoptosis [43]. LPA also stimulates $\alpha_v\beta_6$-mediated TGFβ activation via LPA_2; LPA_2 knockout mice have attenuated injury and fibrotic responses to bleomycin. Upstream of LPA is the enzyme autotaxin (ATX) which is expressed in a variety of cell types including bronchial epithelial cells. ATX is responsible for production of LPA via hydrolysis of lysophosphatidylcholine (LPC) [44,45]. Upregulated ATX expression has been demonstrated in lung tissue from patients with IPF and fibrotic nonspecific interstitial pneumonia (NSIP) but not in organizing pneumonia or non-fibrotic NSIP [46]. ATX knockout mice proved to be embryonically lethal but ATX inhibition via oral medication in adult mouse models was well tolerated and reduced fibrosis in the bleomycin model [45,47].

The effect of inhaled Treprostinil (a prostacyclin agonist) on the pathogenesis of pulmonary fibrosis has been recently evaluated. The interplay between dysregulated pulmonary vasculature and IPF is dynamic with abnormal vascular lesions forming secondary to architectural destruction in IPF while the presence of abnormal vascular lesions also contributes to propagation of fibrosis through endogenous cytokine upregulation. There are multiple prior in vitro and in vivo analyses of downstream signaling pathways related to prostacyclin activation that can account for the impact of Treprostinil on FVC. The antifibrotic mechanism of Treprostinil is likely mediated through a combination of Treprostinil's ability to prevent TGFβ and PDGF fibroproliferative signaling and Treprostinil's affinity for prostaglandin E receptor 2 (EP_2) binding as expression of prostaglandin E_2 (PGE2) inhibits fibroblast proliferation, fibroblast to myofibroblast transition, and collagen deposition [48]. Additionally, Treprostinil binds to prostaglandin D receptor 1 (DP_1) and activation of DP_1 in rodent models of pulmonary fibrosis leads to a reduction in inflammatory cell recruitment and decreased pulmonary collagen deposition [49]. Treprostinil also activates peroxisome proliferator-activated receptor β (PPARβ) via the prostacyclin receptor resulting in retinoid X receptor activation that has downstream anti-inflammatory effects. In a rodent model of bleomycin fibrosis the administration of twice daily orotracheal Treprostinil reduced collagen deposition, parenchymal features of fibrosis, and markers of inflammation, in addition to preserving lung function [50]. Treprostinil promotes vasodilation, reduces pulmonary vascular remodeling, and has a multi-pronged anti-fibrotic effect.

6. Recent or ongoing larger clinical trials in IPF

6.1. $\alpha_v\beta_6$ integrin blockade

There is significant clinical interest in attempting to reduce TGFβ induction by targeting $\alpha_v\beta_6$ integrins. A recent phase IIb study of BG00011, a once weekly subcutaneous anti-$\alpha_v\beta_6$ IgG1 monoclonal antibody, demonstrated that patients receiving 52 mg s.c. weekly of BG00011 actually had worsening of both the FVC and radiologic fibrosis score at week 26 and the study was terminated early [51]. A phase IIa study of the same compound at a higher dose of 1 mg/kg s.c. once weekly resulted in an increase in acute exacerbations of IPF in the treatment group [52]. Approaching $\alpha_v\beta_6$ blockade from a different modality is Bexotegrast (PLN-74809), an oral, once-daily, small molecule dual-selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$. Phase IIa data examining 320 mg of Bexotegrast ($n = 21$) compared to placebo ($n = 8$) showed that by the 24th week 71% of patients in the Bexotegrast arm had stable or improved FVC compared to placebo. Of responders, 50% had an improvement in FVC. Side effects were considered tolerable with 30%

of patients experiencing diarrhea as the main adverse event [53]. The positive results from this study have lead to an adaptive phase IIb/III randomized clinical trial of Bexotegrast that is currently underway.

6.2. Connective tissue growth factor antibodies

Initial enthusiasm for CTGF blockade was driven by a positive phase II trial evaluating the drug Pamrevlumab which is a fully recombinant human monoclonal antibody against CTGF [54]. PRAISE was a multi-center phase II randomized placebo-controlled trial evaluating Pamrevlumab at an infusion dose of 30 mg/kg every 3 weeks over a 48 week period. Background use of anti-fibrotic therapy was not allowed throughout the trial. The study included 103 patients of whom 78 completed the 48 weeks of treatment; there was a significant reduction in the proportion of patients with disease progression (defined as percent predicted FVC change greater than 10% or death) in the Pamrevlumab group compared to placebo. There was also a significant reduction in the HRCT quantitative lung fibrosis score in patients in the Pamrevlumab group. Pamrevlumab was subsequently evaluated in a phase III study of 356 patients with IPF (Zephyrus I); the trial did not meet either the primary endpoint evaluating change in FVC from baseline or the secondary endpoint of difference in time to disease progression. Further evaluation of Pamrevlumab in IPF has been terminated [55,56]. There is however continued interest in CTGF blockade and there is a phase I study in patients with IPF looking at safety of a compound called PRS-220 which is an inhaled Anticalin protein that targets CTGF [56,57].

6.3. PDE4 inhibitor

PDE4 biology has garnered renewed interest particularly given the development of an oral PDE4B inhibitor BI 1015550 that has reduced gastrointestinal side effects compared to older PDE4 inhibitors. BI 1015550 is currently in phase III development following positive findings in a multicenter phase II placebo-controlled trial [58–60]. 147 patients with IPF were enrolled and randomized to BI 1015550 or placebo in a 2:1 ratio. A Bayesian approach to analysis was used to incorporate historic data for the placebo patients from previous trials in the clinical development of nintedanib allowing for fewer overall patients randomized to placebo and increased number of patients randomized to active treatment. Patients with FVC ≥ 45% and DLCO between 25–80% were included in the trial; they were allowed to continue their background antifibrotic therapy but were excluded if on systemic immunosuppression equivalent to 15 mg or greater of prednisone. The primary endpoint was decline in FVC at 12 weeks. 15 patients in the treatment group discontinued BI 1015550 prematurely due to side effects (5 without background antifibrotic use and 10 with background antifibrotics). In the group of IPF patients without background anti-fibrotic use, the median change in FVC at 12 weeks in the BI 1015550 group was +5.7 ml (95% CI, −39.1 to 50.5) and −81.7 ml in the placebo group (95% CI −133.5 to −44.8) with a median difference of 88.4 ml (95% CI 29.5 to 154.2). In the group of IPF with background antifibrotic use the median FVC change at 12 weeks in the BI 1015550 measured +2.7 ml (95% CI −32.8 to 38.2) and −59.2 in the placebo group (95% CI −111.8 to −17.9) with a median difference of 62.4 ml (95% CI 6.3 to 125.5).

6.4. Autotaxin-LPA-LPA$_1$ inhibitors

LPA receptor antagonists are a novel drug therapy that has moved to phase III development [61]. In a phase II trial (NCT01766817) a first generation LPA$_1$ antagonist known as BMS - 986020 was initially evaluated across three arms: placebo, BMS - 986020 600 mg once daily, and BMS - 986020 600 mg po bid. IPF patients with FVC between 45–90% and DLCO between 30–80% were eligible. 143 patients were randomized 1:1:1 and the BMS - 986020 600 mg po bid group demonstrated a statistically significant reduction in rate of FVC decline. The study was terminated early due to liver enzyme elevations and severe gallbladder-related side effects [62]. This led to the development of a second-generation LPA antagonist BMS-986278 with in-vitro and in-vivo evaluation confirming absence of hepatic enzyme elevation. NCT04308681 is a phase II trial of BMS - 986278 in patients with either IPF or PPF in parallel arms randomized 1:1:1 into placebo, 30 mg po daily BMS - 986278, and 60 mg po daily BMS - 986278 [63]. For the IPF arm the trial included patients with FVC > 40% and DLCO > 25%. Background therapy with antifibrotics was permitted; a recent 'forward-looking statement' indicated that in the 60 mg po daily group BMS - 986278 treatment demonstrated a relative reduction in the rate of percent predicted FVC decline of 62%. The medication was well tolerated and there was no difference in adverse events compared to placebo [64]. Also targeting the autotaxin-LPA-LPA$_1$ pathway is a compound called fipaxalparant that functions as a selective allosteric LPAR1 inhibitor and is currently enrolling IPF patients in a phase IIb clinical trial [65]. It was initially studied in management of dermal fibrosis in systemic sclerosis with an 8 week phase IIa placebo controlled trial followed by a 16 week open label extension for all participants most of whom were using background immunosuppressive therapy; the drug was well tolerated with only mild to moderate side effects of headache, nausea, and diarrhea [66]. Two other molecules targeting the autotaxin-LPA-LPA$_1$ pathway include Cudetaxestat (BLD-0409) a differentiated noncompetitive small molecule inhibitor of autotaxin (phase II- not yet recruiting) and BBT-877 a small molecule inhibitor of autotaxin (phase IIa) [67,68]. Enthusiasm for targeting the AUTOTAXIN-LPA-LPA$_1$ pathway may be tempered considering the negative results of phase III RCTs ISABELA 1 and 2 that compared small molecule selective autotaxin inhibitior Ziritaxestat (plus standard of care) with placebo (plus standard of care) in 1306 patients with IPF. The primary outcome of reduced rate of FVC decline was not met and there was an early signal of increased mortality in the Ziritaxestat cohort [69].

6.5. Treprostinil

When Treprostinil received FDA approval as the first treatment for patients with PH-ILD it was a very exciting development in

the pulmonary hypertension world as multiple prior therapies were either unsuccessful or harmful in treating patients with PH-ILD. In a post-hoc analysis of the INCREASE trial, a phase III study exploring inhaled Treprostinil for management of pulmonary hypertension secondary to interstitial lung disease (PH-ILD), there was an unexpected increase in FVC [41–44]. In this trial 326 patients with PH-ILD were randomized 1:1 to receive placebo or inhaled Treprostinil for 16 weeks. Patients started with 3 breaths of 6 µg of inhaled Treprostinil delivered via ultrasonic pulsed-delivery nebulizer and titrated to a target of 9 breaths four times daily with a maximum dose allowed of 12 breaths four times daily. The median dose achieved at the end of 16 weeks was 11 breaths four times daily. Treatment resulted in statistical improvement in 6-minute-walk-distance, reduction in clinical worsening, and reduction in exacerbation of underlying lung disease [70]. In a post-hoc analysis of the pulmonary function data that was collected at baseline, week 8, and week 16 in the INCREASE trial a subgroup analysis of patients with idiopathic interstitial pneumonia showed a significant difference in FVC at week 16 (108.2 ml; standard error 46.9; 95% CI 15.3 to 201.1; $p = 0.023$) as well as a significant difference in percent predicted FVC at week 16 (2.9%; SE 1.1; 95% CI 0.7 to 5.0; $p = 0.0096$) in favor of patients on Treprostinil. When assessing only IPF patients there was a significant difference in FVC at week 16 (168.5 mL; SE 64.5; 95% CI 40.1 to 297.0; $p = 0.011$) and a statistically significant difference in percent predicted FVC at week 16 (3.5% (SE 1.4; 95% CI 0.7 to 6.3; $p = 0{\cdot}015$). Additional analysis of the Treprostinil open label extension trial demonstrated a sustained increase in the FVC for both patients who had inhaled Treprostinil in the initial phase and for patients who started Treprostinil in the open label extension period [71]. The impact of inhaled Treprostinil on the FVC of patients with IPF is currently being explored in two phase III trials over 52 weeks (NCT04708782, NCT05255991) [72,73].

7. Conclusion

The last decade has been punctuated by two exciting advances in the management of IPF with the development of the antifibrotic therapies nintedanib and pirfenidone. These medications have been demonstrated to slow progression in patients with IPF across multiple ethnic and age groups, genders, and severity of lung disease. Unfortunately, they are not curative and they do not reverse established fibrosis. The prognosis for patients with IPF has improved with the adjunct anti-fibrotics but remains overall poor. There have been several encouraging phase II results prompting initiation of phase III studies. What is particularly intriguing at this juncture is that at least one of the four compounds in current phase III analysis (Treprostinil) demonstrated improved FVC rather than simply a reduction in the decline in FVC and it will be very exciting to see if this effect persists.

8. Expert opinion

There has been a growing number of potential therapeutic interventions in IPF with many recent promising early phase clinical trials. Unfortunately, there has been limited positive news from phase III studies. The translation from animal models of fibrosis to human pathophysiology of IPF has been hampered by the fact that there is no spontaneous occurrence of pulmonary fibrosis in these models that progresses over time without an initial inflammatory insult. It is not clear that these rodent models accurately reflect the relentless fibroproliferation encountered in IPF. Not all fibroproliferation is progressive; for example, most patients with acute respiratory distress syndrome (ARDS) encounter an early fibroproliferative phase that eventually resolves and a small minority of surviving patients will develop progressive fibrosing lung disease [74]. Animal models are better in simulating an ARDS phenotype with a component of eventual self-repair rather than an IPF phenotype with multifactorial dysregulated repair. This could account for the success of multiple molecules in rodent models of fibrosis that does not translate into human studies of IPF. The concept of reversing fibrosis with an adaptive repair mechanism is also not well understood from a pathophysiologic perspective and is thus tacitly difficult to target.

The importance of continuing to delineate the role of genetics and mutation analysis in the development and prognosis of IPF cannot be overstated. Precision medicine in patients with IPF is hindered by the uncertain role of various genetic mutations in their protection or promotion of IPF; elucidation of these elements can help target pathways specific to phenotypes associated with an identified mutation which may reduce the number of compounds that fail in phase III studies as the population tested is less entropic [75]. Advancing the understanding of specific genetic factors in the development of IPF will enhance animal models while targeting specific mutation related aberrancy in wound repair or fibrosis proliferation will improve the success of emerging therapeutics in larger phase III analysis [76]. Another promising approach is the augmentation of disease modeling via artificial intelligence and use of human lung tissue to further the goal of human specific drug development [77,78].

Once drug development reaches human stage there is yet to be an adequately validated biomarker to monitor the impact of the therapeutic on the pro-fibrotic milieu in IPF. Easily accessible biomarkers obtained via bronchoalveolar lavage fluid or serum need to be developed and validated, to impact both drug development and disease monitoring. Although there is some desire to lump fibrotic diseases the more resources that are dedicated to refining the diagnoses of interstitial lung disease the more likely a biomarker of significant clinical utility will be identified. The phase III PRECISIONS trial examining the effect of N-acetylcysteine on IPF patients with and without a TOLLIP rs3750920 TT genotype is the first biomarker-driven trial in IPF paving the way toward precision medicine [79].

In concert with developing more robust and informative biomarkers the specific impacts of therapies on disease outcomes (in the form of clinical trial outcomes) should be continuously reexamined. The change in decline of FVC is the primary outcome evaluated in phase III trials but it may be difficult to ascertain due to the need to include background anti-fibrotic therapy. It is important to develop other validated single or composite endpoints. These could involve novel approaches to quantitative lung imaging including artificial

Table 1. Phase III and Phase II clinical trials targeting drug development in IPF.

Target	Compound	Company	Stage of development	Trial identifier
PDE4B inhibitor	BI 1,015,550, Oral	Boehringer Ingelheim	Phase III Active	NCT05321069
LPA1 Antagonist	BMS-986278, oral	Bristol-Myers Squibb	Phase III recruiting	NCT06003426
Prostacyclin analogue	Treprostinil, inhaled	United Therapeutics	Phase III Recruiting	NCT04708782
Mucolytic with anti-oxidant effects	N-acetyl cysteine, oral	Weill Medical College of Cornell University	Phase III Recruiting	NCT04300920
Proton pump inhibitor	Lansoprazole, oral	Norfolk and Norwich University Hospitals NHS Foundation Trust	Phase III Recruiting	NCT04965298
Multitargeted tyrosine kinase inhibitor	Anlotinib, oral	Xiaoying Huang, First Affiliated Hospital of Wenzhou Medical University	Phase III Recruiting	NCT05828953
Inhibits integrins αVβ1 and αVβ6	Bexotegrast (PLN-74809), oral	Pliant Therapeutics	Phase IIb/III Recruiting	NCT06097260
selective antagonist of lysophosphatidic acid receptor-1 (LPAR1)	HZN-825, oral	AMGEN/Horizon Therapeutics	Phase IIb Active	NCT05032066
N-methyl-D-aspartate (NMDA) receptor antagonist	Ifenprodil, (NP-120) oral	Algernon Pharmaceuticals	Phase II completed	NCT04318704
JAK 1, JAK 2 and JAK 3 inhibitor; oral	Jaktinib, oral	Suzhou Zelgen Biopharmaceuticals Co.,Ltd	Phase II Active	NCT04312594
Factor XIIa antagonist monoclonal antibody	Garadacimab (CSL312), IV/SC	CSL Behring	Phase IIa Active	NCT05130970
Angiotensin II type 2 receptor agonist (ATRAG)	C21, oral	Vicore Pharma AB	Phase IIa Active	NCT04533022
Oral, selective Rho Associated Coiled-Coil Containing Protein Kinase 2 (ROCK2) inhibitor	RXC007, oral	Redx Pharma Plc	Phase IIa Recruiting	NCT05570058
Inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) isoforms	Setanaxib (GKT137831) oral	University of Alabama at Birmingham	Phase II Recruiting	NCT03865927
Hedgehog pathway inhibitor	Taladegib (ENV-101), Oral	Endeavor Biomedicines	Phase II Recruiting	NCT04968574
Selectively deuterated form of pirfenidone	Deupirfenidone (LYT-100), Oral	Puretech	Phase II Recruiting	NCT05321420
Autotaxin inhibitor	BBT-877, Oral	Bridge Biotherapeutics	Phase II Recruiting	NCT05483907
Src Tyrosine Kinase Inhibitor	Saracatinib, oral	Astrazeneca	Phase Ia/IIb STOP-IPF Recruiting	NCT04598919
Anti-tumor necrosis factor	Leramistat, Oral	Modern Biosciences	Phase II Recruiting	NCT05951296
Stat-3 Inhibitor	TTI-101, ORAL	Tvardi Therapeutics	Phase II Recruiting	NCT05671835
Prolyl-tRNA synthetase inhibitor	DWN12088 , oral	Daewoong Pharmaceuticals	Phase II Recruiting	NCT05389215
Smurf-1 inhibitor	LTP001	Novartis Pharmaceuticals	Phase II Recruiting	NCT05497284
Human monoclonal antibody against connective tissue growth factor	SHR-1906, IV	Guangdong Hengrui Pharmaceutical Co.	Phase II Recruiting	NCT05722964
human monoclonal oncostatin M receptor β antibody	Vixarelimab	Genentech	Phase II Recruiting	NCT05785624
RNA interference therapeutic targeted toward reducing matrix metalloproteinase 7	ARO-MMP7, inhaled	Arrowhead Pharmaceuticals	Phase I/IIa Recruiting	NCT05537025
Selective thromboxane receptor antagonist	Ifetroban, Oral	Cumberland Pharmaceuticals	Phase II Not yet recruiting	NCT05571059
Differentiated, noncompetitive small-molecule inhibitor of autotaxin	Cudetaxestat (BLD-0409)	Blade Therapeutics	Phase II Not yet recruiting	NCT05373914
Antifibrotic, undefined mechanism	AK3280, Oral	Ark biosciences	Phase II Not yet recruiting	NCT05424887
First in class antifibrotic small molecule inhibitor designed by artificial intelligence	INS018_055	Insilico Medicine Hong Kong Limited	Phase II Recruiting	NCT05975983

intelligence [80]. There has been a growing interest in emphasizing patient reported outcomes in clinical trials as to date few interventions have demonstrated any impact on symptoms or health related quality of life in IPF.

IPF has had a record decade regarding disease investigation, drug development, and global advocacy. The backbone of treatment at present are the antifibrotics nintedanib and pirfenidone which are targeted toward the reduction of progression rather than halting or reversing the fibrotic change. The accompanying Table 1 demonstrates the keen interest that basic scientists, physicians, clinical trialists, patients, caregivers, and pharmaceutical companies have in moving the needle forward on management of IPF. It remains true however that there have been zero successful phase III trials since the introduction of Nintedanib. The review of the literature to date shows promise for novel approaches to the cessation of fibrogenesis as well as repurposing of established drugs for treatment of IPF. The recent success of the outlined pathways ($\alpha_v\beta_6$ integrin blockade, LPA antagonism, PDE4i, and Treprostinil mediated prostacyclin agonism) is tempered by the difficulty of replicating phase II findings in phase III design for IPF patients.

It is an exciting time to be a researcher in the field of IPF but time is of the essence given the continued poor prognosis for patients who do receive a diagnosis of IPF. The next decade will hopefully bring a new wave of treatment options for patients with IPF and renewed hope in altering their survival.

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