Idiopathic Pulmonary Fibrosis: Addressing the current and future therapeutic advances along with the role of Sotatercept in the management of pulmonary hypertension

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with unclear etiology. Clinical manifestations include dyspnea and nonproductive cough. Lung transplantation is the only cure, while Pirfenidone and Nintedanib are FDA-approved drugs for slowing disease progression. However, Saracatinib shows greater efficacy. This literature review assesses the safety and efficacy of IPF treatments, focusing on Pirfenidone and Nintedanib, which preserve lung function and reduce fibrosis and inflammation. We also evaluate emerging treatments such as saracatinib, pamrevlumab, pentraxin-2, BI 1015550, ziritaxestat, PBI-4050, bexotegrast, BMS-986020, TD 139, dasatinib, quercetin, and etanercept. Additional research is needed to explore the therapeutic potential and address gaps in IPF management, including exacerbation and associated pulmonary hypertension (PH). Immunosuppressive agents are used to manage IPF exacerbations, while PH is a recognized comorbidity. Clinical trials, PULSAR and SPECTRA, investigate Sotatercept as a potential PH treatment for IPF patients, showing promising results.

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with unclear etiology. Clinical manifestations include dyspnea and nonproductive cough. Lung transplantation is the only cure, while Pirfenidone and Nintedanib are FDA-approved drugs for slowing disease progression. However, Saracatinib shows greater efficacy. This literature review assesses the safety and efficacy of IPF treatments, focusing on Pirfenidone and Nintedanib, which preserve lung function and reduce fibrosis and inflammation. We also evaluate emerging treatments such as saracatinib, pamrevlumab, pentraxin-2, BI 1015550, ziritaxestat, PBI-4050, bexotegrast, BMS-986020, TD 139, dasatinib, quercetin, and etanercept. Additional research is needed to explore the therapeutic potential and address gaps in IPF management, including exacerbation and associated pulmonary hypertension (PH). Immunosuppressive agents are used to manage IPF exacerbations, while PH is a recognized comorbidity. Clinical trials, PULSAR and SPECTRA, investigate Sotatercept as a potential PH treatment for IPF patients, showing promising results.

Keywords: Idiopathic pulmonary fibrosis, Management, Pulmonary hypertension, Sotatercept

Introduction

Recent understanding of Idiopathic pulmonary fibrosis (IPF) states that IPF is progressive disease of the lung interstitium that is mainly represented by fibrous remodeling of the alveoli as well as gradual loss of pulmonary function that is irreversible. The process is thought to be an accumulation of extracellular matrix (ECM) over a long term. Permanent inhibition of oxygen transfer occurs due to this accumulation, which causes the symptom known as shortness of breath [1]. This problem is seen to develop from the fibrous proliferation and remodeling of tissue due to the faulty signaling and function of alveolar epithelium and fibroblasts of the interstitium. Other factors that have been implicated in the disease pathogenesis included cell-signaling pathways activation by tyrosine kinases such as vascular endothelial growth factor (VEGF). More growth factors include fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF). [2,3]

The major characteristics of the disease are cough and dyspnea which both have a bad impact on the patients in terms of quality of life [4,5] in addition to its effect on life expectancy, with a 3 years median survival when left untreated [6]. What defines IPF is the histopathological and radiological features of lung tissue described as extensive deposition of the ECM that leads to changes in lung architecture, increased alveolar wall thickness, and dilated bronchi [7]. Cases of suspected IPF can be assessed by chest high-resolution CT scan [8,9]. IPF has been found to be the most prevalent type of interstitial lung diseases constituting about 17%–37% of all interstitial lung diseases [10] which makes it mandatory to look for the best treatments possible for the disease. For many years, the management of patients with IPF was only symptomatic and for decades now, the only way to cure IPF is lung transplantation, but in the last decade, multiple drugs have been undergoing clinical trials aiming at better outcomes in IPF patients. Until recently, only two of them have been validated and proven effective in slower progression of IPF, nintedanib and pirfenidone, while other management modalities are still being tested for their effectiveness. In our study, we aim to address the present and future therapeutic agents that reduce pulmonary fibrosis by inhibiting or reducing fibroblast activity or intercept with cell signaling pathway. We aim to provide healthcare professionals with valuable insights to inform their clinical practice and inspire further research in the field of IPF management.

Antifibrotic agents

Pirfenidone

A drug with antifibrotic properties used now for IPF is known as Pirfenidone or PFD, is taken orally [11]. This drug is a synthetic molecule that is small with a characteristic of rapid absorption in the gastrointestinal tract and an estimated 3 hours half-life [12]. Its metabolism is mainly by cytochrome P450, which occurs in the liver and most of it is excreted in the form of 5-carboxy-pirfenidone in urine (80%) or in feces (20%). PFD was found to have two effects on the body, antifibrotic and anti-inflammatory effects [13]. PFD has an inhibitory effect on the proliferation of fibroblasts as well as the synthesis of collagen which is done through interfering with the signaling of transforming growth factor-β, or (TGF-β), and other growth factors, like basic fibroblast growth factor and platelet-derived growth factor (PDGF) [14,15]. It has been shown that PFD is a strong inhibitor of fibronectin and the production of α-smooth muscle actin (α-SMA) which is known to have a role in fibro-myofibroblast transition, when set with TGF-β. PFD has the ability to inhibit TGF-β mediated fibrotic changes in human fetal lung fibroblasts [16,17].

PFD has also shown its anti-inflammatory effect following allergen-induced pre-sensitization, decreasing airway responsiveness, inflammatory cytokines, and cells in the bronchoalveolar fluid [18,19]. Another study revealed that PFD might have the potential to reduce the generation of pro-inflammatory cytokines by stopping the action of p38 MAP Kinase in B lymphocytes, introducing a new potential in PFD for lung fibrosis, as migration and activation of fibroblasts can occur due to the inflammatory process started by B-cell-derived cytokines [20]. While the ASCEND study examined PFD therapy for 52 weeks, the CAPACITY studies assessed its effectiveness and safety for a minimum of 72 weeks. Adverse effects of PFD were found to be mostly photosensitivity, nausea, skin rash, gastrointestinal upset, and anorexia. Serious adverse effects included irregular liver function, facial palsy, dizziness and hepatocellular tumor [21].

The approved dose of pirfenidone that is recommended in Asia is 1800 mg per day, while 2403 mg per day is acceptable in Europe and the US [22]. A study was conducted to evaluate the efficacy of lowered doses of PFD in which the results showed that patients managed with a lower dose of PFD had the same clinical outcomes compared to other patients taking the standard-doses of PFD and so, minimizing the dose could be helpful to maintain the therapeutic efficacy while managing the adverse effects at the same time[22].

Nintedanib

Nintedanib or NDB is taken orally, and has antifibrotic activity by the inhibition of tyrosine kinase receptors like FGFR, PDGFR, and VEGF receptor, and thus inhibiting the signaling pathways of FGF, PDGF, and VEGF which play a pivotal role in the pathogenesis of this disease [23,3]. NDB also has Anti-inflammatory activities although still needs full comprehension. Studies showed that it acts by the inhibition of mediators, including IL-2, 4, 5, 10, 12p70,13, and IF-γ by mononuclear cells in the peripheral blood or T-cells in the human body [24]. NDB was first developed for anti-tumor purposes and was of the first drugs labeled as FDA approved for IPF in the EU and USA along with PFD, after the success of INPULSIS and INSTAGE trials (NDB showed effectiveness in decreasing the decline in FVC) [25-28].

A 150 mg of NDB twice daily dose can provide a therapeutic effect close to the maximum NDB effect regardless of disease condition or demographic baselines for most patients with IPF [29].

Adverse effects of the drug were mainly diarrhea, nausea, nasopharyngitis, cough, and vomiting [30]. As the elimination of the drug is primarily (>90%) biliary/fecal, with a negligible role of renal excretion [31], a lowered dose of 100 mg BID for patients with mild hepatic problems or patients experiencing adverse effects is advised [30].

Potential and Futuristic Drugs in the Management of Idiopathic Pulmonary Fibrosis

Saracatinib

Saracatinib is a specific, strong inhibitor of the Src kinases that was first developed for anti-tumor purposes[32]. Saracatinib has demonstrated that it inhibits the induced increase in the activity of Src kinase

in fibroblasts by TGF-β[32]. Σαραςατινιβ'ς εφφιςαςψ ιν τρεατινγ ΙΠΦ πατιεντς ις ςυρρεντλψ υνδερ ινεστιγατιον βψ α Πηασε 1β/2α ςλινιςαλ τριαλ (ΣΤΟΠ-ΙΠΦ), ας τηε σαφετψ προφιλε ις νοω αλρεαδψ εσταβλισηεδ. Σαραςατινιβ ινηιβιτς σΡϹ ςαυσινγ α δεςρεασε ιν τηε σιγναλινγ πατηωαψ οφ ΈΓΦ, ΦΓΦ, ΠΔΓΦ, ανδ ΕΓΦ φυρτηερ δεςρεασινγ ΡΑΣ αςτιατιον, φιναλλψ λεαδινγ το τηε ινηιβιτιον οφ τηε προλιφερατιον οφ φιβροβλαστς ας ωελλ ας ιτς διφφερεντιατιον (φιγυρε 1).
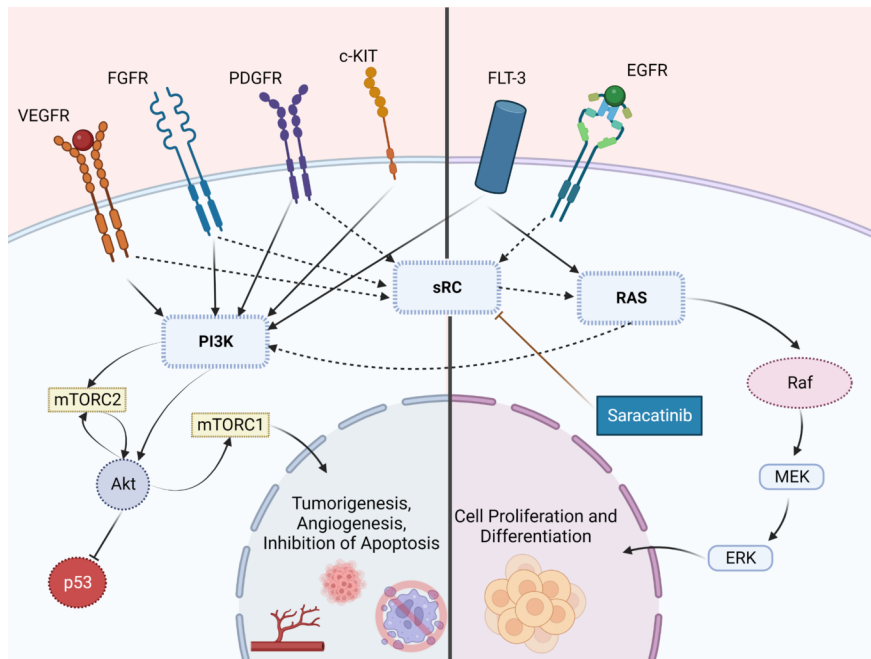

Figure 1. Saracatanib mechanism of action. Saracatinib acts by the inhibition of the SRC protein, resulting in a reduction of signaling pathways. This subsequently diminishes RAS activation, ultimately inhibiting the proliferative activity and the differentiation in fibroblasts. VEGFR; Vascular Endothelial Growth Factor Receptor. FGFR; Fibroblast Growth Factor Receptor. PDGFR; Platelet-Derived Growth Factor Receptor. c-KIT; Tyrosine-protein kinase Kit. FLT-3; FMS-like Tyrosine Kinase 3. EGFR; Epidermal Growth Factor Receptor. sRC; Sarcoma tyrosine kinase. MEK; Mitogen-Activated Protein Kinase Kinase. ERK; Extracellular Signal-Regulated Kinase.

Saracatinib has a larger inhibitory effect than the other two antifibrotic medications on the expression of various profibrotic genes induced by TGF-β, like ACTA2, SERPIN1, and COL1A1, according to an in vitro model research that was conducted with an aim of comparing the efficacy of Saracatinib with the other approved antifibrotic medications. In addition, Saracatinib inhibits TGF-B leading to a change in many signaling pathways, including the JAK-STAT3, IL6, and IFN-γ. It also inhibits the alpha-smooth muscle actin (α-SMA) and filamentous actin (F-actin). All of these inhibitory effects prevent fibroblast transformation to myofibroblast as well as decrease pulmonary collagen deposition [32].

In a precision cuts lung slices or PCLS conducted for complementary purposes, saracatinib had a much better effect than NDB and PFD by studying an *ex vivo* model showing reduction in pulmonary fibrosis and this was confirmed in *in vivo* mouse models. Therefore, this study provided an absolute indication that saracatinib is equal or could be even better than the currently used antifibrotic drugs, PFD and NDB as an inhibitor of pulmonary fibrosis in experimental models [32], showing a potential that it could replace both drugs in the future.

Table 1. Comparison between Saracatinib, Nintedanib, Pirfenidone   **Table 1. Comparison between Saracat**

Comparison aspect	Saracatinib
Mechanism of action	Src kinase inhibitor.
TGF- ? expression of profibrotic genes.	Larger inhibitory effect including ACTA2, C
TGF-β-induced Smad3 phosphorylation	Inhibitory effect.
Experimental pulmonary fibrosis reduction	Better effect.
Precision cuts lung slices results	Better effect in reducing pulmonary fibrosis

TGF-?; Transforming Growth Factor-beta, MAPK; Mitogen-Activated Protein Kinase, ACTA2; Alpha Smooth Muscle Actin, COL1A1; Collagen Type I Alpha 1 Chain.

Pamrevlumab

A recombinant antibody called pamrevlumab has the capability to recognize the connective tissue growth factor (CTGF), binds to it, and therefore stops it from cytokines binding, thus avoiding following inflammatory signaling [33]. The CTGF is released by multiple types of cells like fibroblasts, myofibroblasts, and endothelial cells and it's a glycoprotein . It is thought CTGF has interactions with different regulators, like TGF-β, VEGF, and integrin receptors. This way, CTGF regulates the response of cells to the environment, such as secretions, sorting, production of ECM, motility of cells, and adhesion. These biological processes have been linked to cancer formation and abnormal tissue healing, including fibrosis [34]. PRAISE trial (a phase 2 trial) showed in 2019 that pamrevlumab taken intravenously decreases the decline in FVC successfully by 70% in approximation in patients with IPF in comparison with those receiving placebo[34]. Interestingly, the benefits from the treatment were seen, unlike any other trials, in spite of whether the change in FVC was expressed as an alteration in percentage predicted values, volume change, or in a categorical analysis of free-of-progress survival as the majority component[35]. The impact of treatment was noticeable with equal treatment effects in radiological and symptomatic parameters, which was not found in other studies, yet the results should be treated cautiously until an appropriately powered phase 3 investigation is done [34]. This study's findings are perhaps on the top of phase 2 trials results, and whether pamrevlumab's therapeutic advantages might be enhanced with the administration of antifibrotic medications is now under studies[35,36].

Pentraxin-2

The naturally occurring protein called pentraxin-2 has a recombinant form, named recombinant human pentraxin-2 (rhPTX-2; aka PRM-151). This drug is being investigated for its potential to be a probable option in IPF treatment. A phase II trial, which was a double-blind randomized, placebo-controlled PRM-151-202 portion research that tested rhPTX-2 in patients with IPF (NCT02550873), has shown results that are now published [37]. When compared to placebo, rhPTX-2 considerably slowed the decrease in FVC and stabilized 6-min walk distance (6MWD) after receiving the drug, according to the placebo-controlled study of PRM-151-202 [37]. For those patients receiving either PFD or NDB with it, as well as individuals receiving rhPTX-2 monotherapy, efficacy patterns of rhPTX-2 were seen [37]. This Phase II study's observation of rhPTX-2's impact on 6MWD was novel because this is the first time a clinical trial for IPF uses a 6MWD to demonstrate the stability of functional status of patients[37, 38].

In the group taking the medication, a decrease in the drop in the mean percent predicted FVC and 6MWD in meters was shown, and this was maintained for up to 52 weeks[37,39]. When patients started taking Pentraxin-2 during the extension phase of the study, the percent of their FVC decline was enhanced from 8.7% a year to 0.9% a year and their 6MWD leveled up from 54.9 meters a year to 3.5 meters a year. However, the long-term consequences of IPF were still consistent with the results, occurring in about 28% of patients [39]. These results will be explored more in a 52 week Phase III research of rhPTX-2 (STARSCAPE), a long term OLDE study will also follow the phase III trial, in order to evaluate the clinical importance. If the results of the Phase III study are consistent with the results of Phase II trial, rhPTX-2 could be very promising as an adjunctive option to current antifibrotic drugs to delay IPF progression as well as an efficient monotherapy option in patients who are unable to tolerate the available choices [39].

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BI 1015550

One of the drugs that are now being investigated is the inhibitor of phosphodiesterase 4 group, BI 101550. Phosphodiesterase 4, or PDE4, is described by proteins which play crucial roles in the cells of a human being. Drugs that suppress PDE4 activity have been demonstrated in prior research to reduce inflammation and scarring.[40] Inhibition of PDE4 leads to the inhibition of fibroblast action, further preventing the transformation of fibroblast to myofibroblast. PDE4 group has many functions, inhibiting all of its functions could be problematic as it may cause side effects. This drug primarily works on PDE4B, and it is anticipated by researchers that this will decrease the likelihood of side effects. A phase II double-blinded, randomized study was done and the drug BI 1015550 was examined for having the potential to become an option in managing IPF. The study compared the placebo with BI 1015550 [40]. In total, 147 IPF patients from 22 different countries participated in the trial. The findings demonstrated that BI 1015550 protected IPF patients' lungs function from deteriorating. With BI 1015550 or placebo, no difference was seen in patients with medical conditions the study physician classified as severe. However, diarrhea affected more persons who received BI 1015550 treatment. Thirteen patients receiving BI 1015550 had to stop their treatment because of health problems; none of the patients receiving a placebo had to stop their treatment because of health problems [40].

Ziritaxestat

Lysophosphatidic acid (LPA) is hypothesized to at least in part mediate the abnormal wound healing responses that lead to fibrosis that is seen with IPF. IPF patients have higher levels of LPA and the enzyme responsible for its formation, autotaxin (ATX), demonstrating their involvement in the etiology of the disease and suggesting possible targets for novel therapeutics [41].

A phase IIa research was done involving 23 IPF patients. Ziritaxestat, which is a small-sized molecule of selective autotaxin inhibitor [42,43], demonstrated promising outcomes [44]. When compared to placebo at week 12, those on ziritaxestat showed a reduced change in FVC. Ziritaxestat here was well tolerated. Ziritaxestat also decreased plasma LPA concentration, showing a maximal decline from baseline of almost 90%, indicating target reach [44]. Phase 3 of two randomized clinical studies, ISABELA 1 and 2, with identical designs, had been done to further assess the effectiveness and safety of ziritaxestat in IPF. In this trial, in patients getting treatment with PFD or NDB or in those not receiving the PFD/NDB treatment, ziritaxestat did not prove to have a better clinical outcome compared to placebo [45]. That's part of the reason why the ISABELAs failed, which needs to be looked into more. This could be looked into by continuing research on other autotaxin inhibitors, such as BBT-87723, or LPA receptor antagonists, such as BMS-98627824, which have different pharmacological properties from those in ziritaxestat. It should be noted that the LPA receptor antagonist (BMS-986020) was halted because of the resultant hepatobiliary toxicity, but it was later determined that this was unrelated to LPA antagonism [46, 47] in fact, no such safety concerns were detected in the ISABELAs.

PBI-4050

PBI-4050, which is an orally active low molecular weight chemical considered first-in-class, is being tested in trials for the treatment of disorders of fibrosis including IPF. It is the sodium salt of 3-pentylbenzeneacetic acid. It is an artificial form of a medium-chain fatty acid that binds to the G-protein coupled receptors GPR40 and GPR84 with agonist and antagonist affinities, respectively. By regulating fibroblasts/myofibroblasts, macrophages, and epithelial cells, it can reduce or reverse fibrosis [48]. By interacting with GPR40 and GPR84, PBI-4050 stops the progression of fibrosis by regulating a number of anti-fibrotic pathways through this interaction connected to the emergence of IPF [48]. The absence of the expression of alpha-smooth muscle actin in fibroblasts and the concomitant increase of ECM deposition and fibrosis are an evidence that the drug prevents the differentiation of fibroblasts into myofibroblasts. Monocyte chemoattractant protein-1, IL 8 and 6 which have the major role in inflammatory processes in addition to CTGF which has a major role in developing IPF all had been decreased by PBI-4050 [48]. PBI-4050 also dramatically reduces fibrosis in bleomycin-induced lung fibrosis in a murine model as well as models in the heart, liver, lung, kidney,

pancreas, and skin [48]. The drug caused a 47% reduction in lung tissue disruption, fibrosis, as well as alveolar wall thickness [48]. According to these findings, PBI-4050 may have clinical benefits for fibrotic disorders like IPF. A phase II single-arm open-label research (NCT02538536) was carried out for 12 weeks at six sites across Canada in people with IPF [49]. The main goal of this study was to assess PBI-4050's safety and tolerability in this patient population. The findings of this trial demonstrated that there were no safety concerns following 12 weeks of management in patients with primarily mild to moderate IPF, whether used as monotherapy or combined with nintedanib or pirfenidone. PBI-4050's PK profiles were identical when used alone and in conjunction with nintedanib, but they were altered when combined with pirfenidone, pointing to a potential interaction between drugs. FVC outcomes for PBI-4050 by itself and when combined with nintedanib were promising [49].

Bexotegrast

Or PLN 74809, an oral small molecule had been confirmed in vivo to have antifibrotic by inhibiting dual αvβ6/αvβ1 integrin (important mediators of activation of TGF-β in fibrosis), this results in the partial inhibition of the TGF-β signaling pathway. By this mechanism of action, Bexotegrast can be used for the reduction of systemic side effects and toxicities produced by the full TGF-β signaling pathway inhibition in the treatment of IPF, as well as inhibiting the expression of mRNA collagen [50]. A phase IIa, open, four-part, double-blind, randomized, placebo-controlled study known as INTEGRIS-IPF is now investigating the safety, tolerability, and pharmacokinetics of PLN 74809. Good efficacy, safety, and tolerance were shown by PLN 74809. For all patients receiving PLN-74809, the average decrease in FVC was 15.1 mL in contrast to 74.1 mL for individuals receiving the placebo. With larger doses of the medication, the FVC decline was improving, and in line with the encouraging outcomes seen thus far for larger doses, Pliant has disclosed a trial extension that assesses the effectiveness of 320 mg of PLN-74809 administered daily for six months to persons with IPF. Early in 2023, preliminary trial results ought to be made public [51].

BMS-986020

In a phase II study, the first generation drug, BMS-986020, which is an oral LPA1 antagonist, showed mechanism proof in patients with IPF [52]. In general, BMS-986020 decreased FVC decline during the course of 26 weeks when compared to placebo, with substantial changes occurring after 600 mg twice daily (BID) treatment. BMS-986278 which is the second generation of LPA1 antagonist, is being developed to treat people with IPF. In contrast to BMS-986020, in vitro research demonstrates that BMS-986278 shows no inhibitory effect on the transporters of liver efflux, specifically the multidrug resistance 3 (MDR3) and the bile salt export protein (BSEP). Additionally, in vivo testing and phase 1 studies have not revealed any signs of direct hepatobiliary toxicity.[53,54] This phase II trial's aim is to assess BMS-986278 in IPF patients or IPF-ILD patients given that the antagonism of LPA1 was proven to be helpful in IPF patients.

TD 139

The expression of galectin (Gal)-3, a key regulator of lung fibrosis, is raised in the lavage fluid and serum of the bronchi and alveoli of IPF patients, and this expression is further elevated during acute phases.[55, 56] In mouse models of pulmonary fibrosis, TD139, a Gal-3 inhibitor with a strong affinity for the carbohydrate recognition domain of Gal-3, has demonstrated effectiveness [55, 56]. The key to TD139's antifibrotic potential is the inhibition of recruitment and growth of Gal-3-secreting macrophages, which promote local myofibroblast activation, [57, 58]. Preclinical studies have demonstrated that TD139 is effective on all of the major IPF cell types, including fibroblast activation,Gal-3/Macrophage phenotype expression, a reduction in the activity of important profibrotic growth factors on myofibroblasts, and epithelial-mesenchymal transition inhibition[55,56,58]. A phase 1/2a, multicenter, randomized trial conducted in the UK assessed the effectiveness of TD 139. With the exception of TD139 being less preserved in the lungs of patients with IPF, the pharmacokinetic characteristics were basically similar between the healthy and IPF participants. Additionally, TD139 was found to have good tolerance by both healthy people and IPF patients, with the most common side effects being disturbance of taste (36.1%) and cough (11.1%). No significant changes on clinical terms were found in electrocardiographs, nor any hematological, biochemical markers, or clinical

findings [59].

Dasatinib (D) and Quercetin (Q)

Animal models have been used to carry out cellular senescence targeted senotherapeutic medications, and they have shown better and functional status [60,61]. Senescent cell anti-apoptotic pathways or SCAPs are inhibited by senolytics, which kill senescent cells in a targeted manner. Dasatinib with quercetin (D & Q), when combined synergistically, were the first medicines regarded as senolytics discovered in 2015 under the direction of Zhu et al [62]. Dasatinib is originally a chemotherapeutic medication for the management of chronic myeloid leukemia that shows resistance to imatinib, another tyrosine kinase inhibitor. It inhibits numerous tyrosine kinases with broad targeting of Src kinases in its action. Quercetin on the other hand, is a non-synthetic and non-specific kinase inhibitor that works on PI3K/AKT pathways, in addition to BCL-2, insulin/IGF-1, and HIF-1 SCAPs components. It also show a senolytic action, presumably as a result of the inhibition of many SCAP genes (like PI3K and other kinases), and it targets a number of SCAPs pathways.[62,63,64] When taken together, D + Q are complementary and result in greater senolysis. They also reduce the burden of senescent cells and human tissue SASP after two days of administration.[62,65] In order to make it easier to organize larger efficacy trials, an affirmative randomized, placebo-controlled study of D+Q in IPF patients was conducted to assess the efficacy and ability to tolerate of D + Q compared to placebo. The prescribed drug dosage schedule (108/108 doses) and the intended assessments (60/60) were completed by all participants. No significant side effects connected to D + Q were addressed, despite the fact that the placebo contained fewer total mild AEs. The majority of AEs with D + Q treatment are typical in patients with IPF or expected D AEs. Anxiety and sleep problems were overrepresented in the D + Q treatment. Before and after intermittent D + Q, fragility, pulmonary function, and physical function were examined; although underpowered to detect differences, these variables do not seem to be significantly different across groups. It is possible and typically well tolerated to provide D + Q intermittently to people with IPF. To establish the safety and effectiveness of D + Q in IPF patients, additional research, like a bigger RCT, is required.

	Table 2. Summary of the newer modalities in the treatment of IPF	Table 2. Summary
Name	Name	**Mechanism of a**
Pirfenidone	Pirfenidone	TGF-? and fibron
Nintedanib	Nintedanib	Tyrosine kinase in
Saracatinib	Saracatinib	Src kinase inhibit
Pamrevlumab	Pamrevlumab	CTGF inhibitor
Pentraxin-2	Pentraxin-2	Recombinant hum
BI 1015550	BI 1015550	phosphodiesterase
Ziritaxestat	Ziritaxestat	selective autotaxi
PBI-4050	PBI-4050	interacting with G
Bexotegrast	Bexotegrast	inhibitor of integr
BMS-986020/ BMS-986278	BMS-986020/ BMS-986278	LPA1 antagonists
TD 139	TD 139	Gal-3 inhibitor
Dasatinib (D) and Quercetin (Q)	Dasatinib (D) and Quercetin (Q)	Senescent cell anti

TGF-?; Transforming Growth Factor-beta, CTGF inhibitor; Connective Tissue Growth Factor inhibitor, GPR40; G-protein-coupled receptor 40, GPR84; G-protein-coupled receptor 84, LPA1 antagonists; Lysophosphatidic Acid 1 Antagonists.

Symptomatic treatment of IPF

There aren't many well-powered trials that have been done, hence managing an IPF exacerbation is not yet reported. Most respiratory doctors test pulsing of methylprednisolone (0.5 - 1 g a day over three days), while anecdotal reports have also mentioned the use of cyclophosphamide and rituximab[66]. Although often used,

intravenous steroids have not been the subject of a randomized, placebo-controlled trial. The responsiveness to corticosteroids based on accumulating dose in IPF acute phases was examined in a retrospective trial. Higher doses of steroids were favorable in ILDs except in IPF, according to the authors [67]. However, in a different investigation, steroid treatment in the acute phase of IPF was linked to greater death rate[68]. One more retrospective study demonstrated that early reduction of steroids after pulses provided superior results [69]. Corticosteroid therapy had a negative influence on IPF patients, especially on diabetes and osteoporosis [70], as well as in randomized, double-blind, placebo-controlled trials that have clarified that adding prednisone to azathioprine and N-acetylcysteine (NAC) increases mortality rate [71], so corticosteroids aren't recommended to patients with IPF, as it is known that the corticosteroids have anti-inflammatory effect and recent studies have shown IPF's secondary role of inflammation in addition to the primary role of fibrosis in the pathogenesis of IPF [71], so we recommended in using antifibrotic agents instead of anti-inflammatory agents in IPF. Regardless of the paucity of high-quality proofs, the most recent updates of IPF management guidelines continue to recommend using steroids in the treatment of acute phases[72]. Prospective randomized trials are therefore required. Other immunosuppressive medications are frequently used in some nations [71].

The Role of Sotatercept in the Treatment of Pulmonary Hypertension in IPF

There is an urgent need for better treatments of pulmonary hypertension (PH) in the context of IPF since patients with advanced ILDs who also have coexisting pulmonary vascular disease have worse outcomes than they would have with either diagnosis alone [72].

A newly developing fusion-protein, named sotatercept, attempts to balance pro- and anti-proliferative (BMPR-II- and ActRIIA-mediated) signals by binding to and sequestering a subset of TGF superfamily ligands (figure 2). Sotatercept has been demonstrated to stop right ventricular remodeling and pulmonary arterial wall remodeling in PH preclinical models [73]. Sotatercept largely reduced vascular resistance in the lungs in patients with PH on background therapy in a phase 2 trial (NCT03496207), and for now, sotatercept is the subject of operating clinical studies (NCT03738150, NCT04576988, NCT04811092, NCT04896008).
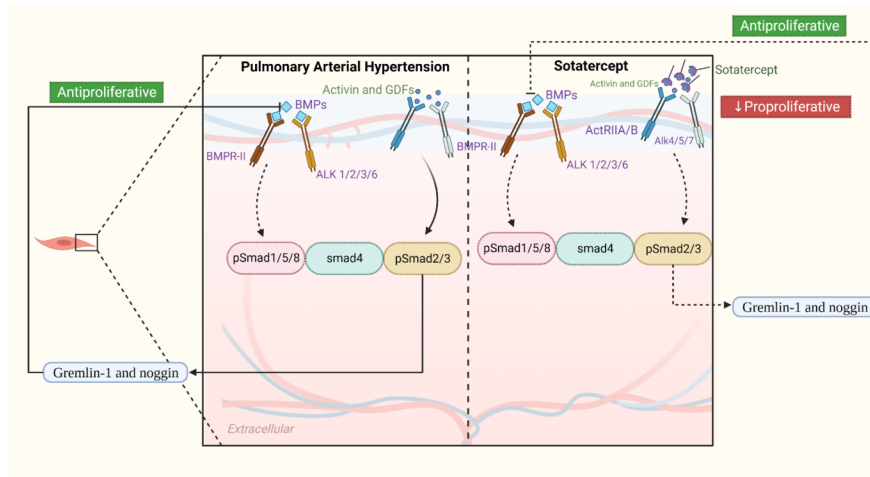

Figure 2. Proposed Mechanism of Action for Sotatercept in Pulmonary Arterial Hypertension. The proposed mechanism of action for Sotatercept involves rebalancing growth-promoting and growth-inhibiting signaling in pulmonary arterial hypertension. This condition is characterized by dysregulation of the BMP receptor type II (BMPR-II)–Smad1/5/8 pathway in pulmonary vascular smooth muscle and endothelial cells, resulting in an imbalance between proproliferative and antiproliferative signaling pathways. Down-regulation of the BMPR-II–Smad1/5/8 pathway leads to increased production of activin ligands (e.g., activin A, GDF8, and GDF11), which in turn up-regulate the ActRIIA–Smad2/3 pathway. This pathway activation, indicated by increased phosphorylated Smad (pSmad)2/3 activity, promotes the expression of endogenous BMP antagonists,

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gremlin-1 and noggin. Gremlin-1 and noggin subsequently reduce BMP–Smad1/5/8 signaling, resulting in a decrease in antiproliferative signaling. This shift favors proproliferative activin–Smad2/3 signaling, leading to pulmonary vascular remodeling.

A significant clinical research program involving patients with PH, including the phase 2 PULSAR project, is evaluating the clinical effectiveness and safety of sotatercept when it's added to PH medication [74, 75]. The sotatercept medication significantly decreased pulmonary vascular resistance (PVR) during the 24-week placebo-controlled treatment phase of the PULSAR study from baseline, when compared to placebo. In addition, in comparison with placebo, sotatercept increased the levels of the 6MWD and the N-terminal pro-B-type natriuretic peptide (NT-proBNP).

An ongoing innovative exploratory investigation called the SPECTRA project (NCT03738150) aims to assess the influence of sotatercept by invasive cardiopulmonary exercise testing (iCPET). Hemodynamics, exercise tolerance, and capacity showed encouraging outcomes in this preliminary examination of participants in the continuing SPECTRA trial. Safety was comparable with other reports in patient populations with PH and other conditions. These outcomes emphasize the sotatercept's clinical effectiveness and potential as a brand-new therapy for PH patients [76].

Conclusion

Recent understanding of Idiopathic Pulmonary Fibrosis (IPF) reveals it as a progressive disease of the lung interstitium, characterized by fibrotic alveolar remodeling and irreversible loss of pulmonary function. While previous management was symptomatic, recent clinical trials have focused on developing effective treatments. Current modalities include antifibrotic agents (nintedanib and pirfenidone) and promising options like Saracatinib, pamrevlumab, and rhPTX-2. Investigational therapies such as BI 1015550, ziritaxestat, PBI-4050, PLN 74809, BMS-986020, and TD139 require further evaluation. The combination of dasatinib and quercetin shows potential as a senolytic therapy. Ongoing research is crucial for the assessment of the efficacy, safety, and use of these treatments in the management of IPF. Sotatercept has demonstrated positive outcomes in preclinical models and trials for treating PH in IPF patients, reversing remodeling and reducing pulmonary vascular resistance. The SPECTRA trial supports its effectiveness, but more studies are required for the evaluation of its efficacy and safety. Managing IPF exacerbations is challenging due to limited guidelines. High steroid doses and pulse methylprednisolone lack strong evidence and may harm AE-IPF cases. Retrospective studies suggest early steroid reduction for better outcomes, though current guidelines still recommend their use. Conversely, immunosuppressive medication like cyclophosphamide has shown unfavorable outcomes and increased mortality rates in trials. Advancements in IPF treatment hold promise for improving patient outcomes, but ongoing research and trials are essential to fully evaluate the safety, efficacy, and practical application of those treatments in IPF management.

List of abbreviations

AKT – protein kinase B

α-SMA – alpha-smooth muscle actin

Col1 – type I collagen

CCL20 – chemokine ligand 20

CTGF – Connective tissue growth factor

ECM – Extracellular matrix

ERKs – Extracellular signal-regulated kinases

FGF – Fibroblast growth factor

FLT3 – FMS-like tyrosine kinase 3

FVC – Forced vital capacity

GPR – G-protein-coupled receptor

HRCT – High-resolution computed tomography

iCPET – Invasive cardiopulmonary exercise testing

IPF – Idiopathic pulmonary fibrosis

KIT – Receptor Tyrosine Kinase proto-Oncogene

LPA1 – Lysophosphatidic acid receptor 1

NDB – Nintedanib

NT-proBNP – N-terminal pro-B-type natriuretic peptide

PDE4 – Phosphodiesterase 4

PDGF – Platelet-derived growth factor

PFD – Pirfenidone

PH – Pulmonary hypertension

PVR – Pulmonary vascular resistance

TGF-β – Transforming growth factor-β

VEGF – Vascular endothelial growth factor

Data availability:

The authors confirm that the data supporting the findings of this study are available within the article.

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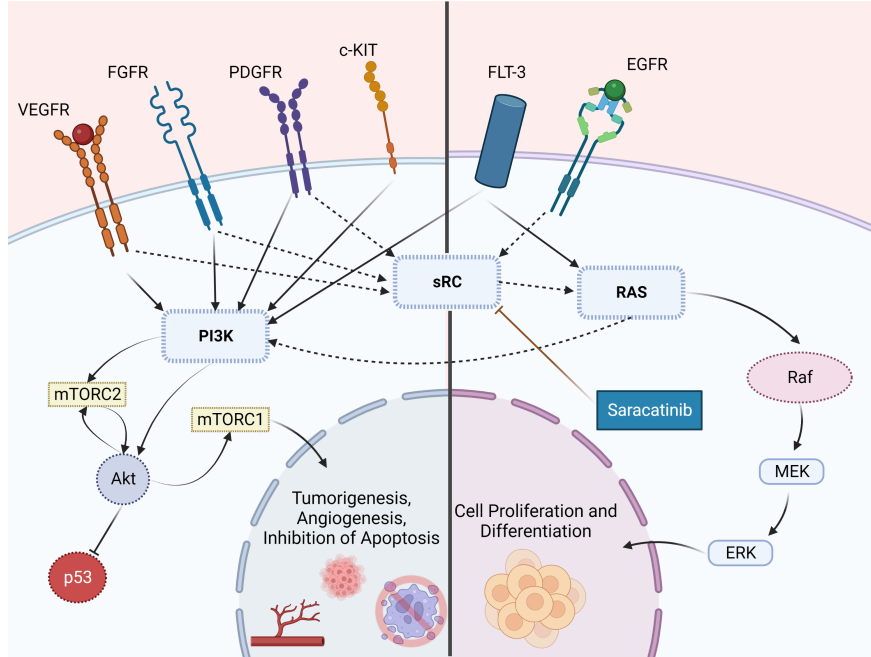
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