Chapter

Pharmacological Management of Idiopathic Pulmonary Fibrosis

Ladan Panahi, George Udeani, Andrew Scott Tenpas, Theresa Ofili, Elizabeth Marie Aguilar, Sarah Burchard, Alexandra Ruth Ritenour, April Jacob Chennat, Nehal Ahmed, Chairat Atphaisit, Crystal Chi, Jesus Cruz III, Monica D. Deleon, Samantha Lee, Zack Mayo, Mackenzie Mcbeth, Mariel Morales, Jennifer N. Nwosu, Kelly Palacios, Jaycob M. Pena and Nitza Vara

Abstract

Idiopathic pulmonary fibrosis (IPF) is a common interstitial lung disease (ILD) caused by environmental exposures, infections, or traumatic injuries and subsequent epithelial damage. Since IPF is a progressively fatal disease without remission, treatment is both urgent and necessary. The two medications indicated solely for treatment include the tyrosine kinase inhibitor nintedanib (Ofev®) and the anti-fibrotic agent pirfenidone (Esbriet®). This chapter discusses in detail the current treatment options for clinical management of IPF, specifically the mentioned two pharmacotherapeutic agents that decrease physiological progression and likely improve progression-free survival. The chapter also discusses the evolution of drug therapy in IPF management and the drawbacks and limitations learned throughout historical trials and observational studies.

Keywords: drug therapy, pharmacological management, idiopathic pulmonary fibrosis, review

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a common interstitial lung disease (ILD) caused by environmental exposures, infections, or traumatic injuries and subsequent epithelial damage [1, 2]. It is characterized by fibroblast activation, followed by excessive secretion of extracellular matrix in the bronchial walls and alveolar interstitium [3]. This uncontrolled deposition leads to stiffening of lung tissue, which impairs diffusion of gases and reduces blood oxygenation [3, 4]. More prevalent among males and adults over 65 years old, it has a high incidence in North America and Europe [1]. Smoking, family history, and genetic mutations associated with telomere length maintenance have been linked to increased risk of developing IPF, as well as the history of gastroesophageal reflux disease and obstructive sleep apnea [1].

Patients typically present with chronic, progressive dyspnea, and dry cough [5]. Their history may include long-term smoke or workplace exposure such as inhalation of wood or metal particulates [6]. On physical examination, bibasilar inspiratory crackles ("velcro rales") and finger clubbing may be seen [4, 7]. Pulmonary function tests (PFTs) usually demonstrate reduced lung capacity and reduced diffusion capacity for carbon monoxide, indicating restrictive disease and abnormal gas exchange [4, 8]. Exclusion of other interstitial lung diseases—including autoimmune diseases—is required before a diagnosis can be made. Additionally, the presence of a honeycomb fibrosis pattern on high-resolution computed tomography is necessary [4, 8]. Patients commonly have at least one comorbidity, such as chronic obstructive pulmonary disease (COPD), pulmonary hypertension, lung cancer, and diabetes mellitus [4, 8].

IPF is characterized by irreversible and potentially fatal lung deterioration [8, 9]. Patients may experience different rates of disease progression, ranging from gradual deterioration to stable periods lasting months or years. Symptoms associated with progression include worsening dyspnea, hypoxemia, and pulmonary hypertension, as well as fatal exacerbations, where respiratory function declines acutely and unpredictably [8, 9]. Although the disease course varies among patients, prognosis remain poor, with an average life expectancy of 3–5 years after diagnosis [4, 9].

2. Standards of care

Since IPF is a progressively fatal disease without remission, treatment is both urgent and necessary [10, 11]. The two medications indicated solely for treatment include the tyrosine kinase inhibitor nintedanib (Ofev®) and the anti-fibrotic agent pirfenidone (Esbriet®) [4, 12]. Both were approved in 2014 after clinical trials suggested that they halted the decline in lung function, including a decline in forced vital capacity (FVC) by 50% over a 1-year period [4, 11]. Moreover, they have been shown to be safe and effective in reducing severe respiratory episodes often seen in IPF [4].

Treatment regimens for COPD, heart disease, and smoking cessation are also recommended to reduce respiratory strain if experienced concurrently [4, 13]. Patients suffering from hypoxemia and IPF often receive supplemental oxygen [4, 14]. Pulmonary rehabilitation, physical therapy, and oxygen are all recommended to improve exercise tolerance and duration, reduce dyspnea, prevent the development of pulmonary hypertension, and improve overall lung capacity [4].

Lung transplantation remains a viable option for those who meet the criteria for the procedure [11]. It must be considered earlier in disease progression, with early evaluation to maximize eligibility [4, 11]. Past treatments like warfarin, N-acetylcysteine, prednisone, and azathioprine are no longer recommended due to an overall lack of treatment efficacy [4, 15]. Furthermore, these pharmacotherapeutic options should be avoided in IPF until high-quality randomized control trials prove efficacy since they have failed to show relevant reductive changes in FVC, adverse events, or death [16].

3. Non-pharmacological management and supportive care

Though current drug therapies demonstrate a reduction in acute exacerbations due to their cytotoxic and immunosuppressive side effect profiles, non-drug measures are often considered. Unfortunately, patients opting for mechanical

ventilation—often as a bridge to lung transplantation—suffer from low survival rates [17]. Poor prognostic indicators include a decline in 6-minute walk (6 MW) distance greater than 150 meters within one year, a decrease in FVC greater than 10% within 6 months, and a decline in diffusing capacity for carbon monoxide (DLCO) greater than 15% within 6 months [4].

Improvements in both quality of life and 6 MW distance can be seen in those undergoing pulmonary rehabilitation [4]. Length of survival is highly variable; patients diagnosed with mild, moderate, and severe diseases survive an average of 55.6, 38.7, and 27.4 months, respectively [4]. Ultimately, transplantation remains the only option for those with advanced IPF; those who do not undergo this procedure often have poorer outcomes [4, 12]. Approximately 66% of transplant recipients live for more than 3 years postsurgery, while 53% survive greater than 5 years [4]. Transplantation does carry certain complications such as cancer, infections, primary graft dysfunction, cytomegalovirus, and allograft rejection are all commonly seen [12]. Moreover, supplemental oxygen has been shown to improve symptom control during exercise, while lung transplantation may increase survival rates and improve patients' overall quality of life [14].

Since drug therapy is merely supportive therapy, patients are encouraged to take alternative measures to decrease their risk, including smoking cessation, supplemental oxygen, and pulmonary rehabilitation [4]. Ongoing GERD has been thought to worsen IPF, but the use of antacids based on clinical trials remains inconclusive [4]. Although the relation of GERD to IPF is still unknown, the prevalence of GERD and erosive esophagitis are observed more commonly in patients with IPF than in the general population [18, 19].

Lastly, patients should receive pneumonia and influenza vaccinations as part of complementary therapy, though there is no proven benefit for the previously mentioned interventions [14]. Although there is no documented outcome benefit with vaccination in the IPF setting, preventing pulmonary infections is essential as extrapulmonary comorbidities through interactions with environmental factors by various mechanisms are thought to contribute to IPF [20]. Vaccinations are especially recommended for post-transplantation patients since they may be more susceptible immunologically. In outpatient settings, pulmonary hypertension should be controlled with supplemental oxygen [21]. Unless a patient participates in a clinical trial, alternative therapies should be avoided.

4. Previous therapies

Although commonly used for their anti-inflammatory effects, corticosteroids do not improve clinical outcomes in IPF [14, 22]. When used as monotherapy, they show no survival benefit and actually increased risk of morbidity with long-term use [7, 14]. A regimen consisting of prednisone, azathioprine, and N-acetylcysteine (NAC) was once accepted therapy [7, 14]. However, trial data revealed that, compared to placebo, the combination increased risk of death and hospitalization [7, 14].

Ambrisentan (Letairis®), a potent type-A selective endothelin receptor antagonist, was once thought to decrease time to disease progression [7]. However, the ARTEMIS-IPF trial examined its use in IPF patients, finding it to be ineffective and associated with increased risk of hospitalizations and disease progression [7]. The trial was eventually terminated when an interim analysis found minimal efficacy [7]. Recent guidelines no longer recommend the anticoagulant warfarin since it was associated with a higher risk of mortality compared to placebo [7, 14].

5. Current therapy: nintedanib

After numerous studies yielded conflicting results, new treatment options were developed, including two novel anti-fibrotic agents capable of slowing disease progression [4]. Pirfenidone and nintedanib both demonstrated a significant reduction in annual FVC decline and improved survival [7].

Nintedanib (Ofev®), an oral tyrosine kinase inhibitor, inhibits the fibroblast proliferation leading to progression of lung fibrosis [3, 4]. It may also inhibit other growth factor receptors, including tyrosine kinase vascular endothelial growth factor receptor and platelet-derived growth factor receptor [3, 4, 7]. This multi-faceted inhibition makes it a first-line agent for IPF [3, 7]. The standard dose is 150 mg twice daily taken with food to increase bioavailability [4, 7]. However, dosing can be withheld or lowered to 100 mg twice daily if side effects become intolerable [7]. Once controlled, standard dosing can be resumed [7]. If adverse reactions persist, however, discontinuation should be considered [7]. The most common side effects associated with its use include diarrhea, nausea, and vomiting [7]. Other important side effects include weight loss and drug-induced hepatotoxicity, designated by a 3–5 fold increase in AST/ALT, with or without severe liver damage. Discontinuation or dose reduction is based on the presence of severe liver damage; details relating to specific therapeutic steps can be found in **Table 1**. Adverse reactions should be monitored alongside signs of increased bleeding, especially in those taking anticoagulants.

Bioavailability	**5%** **Increases by 20% when given with food**
Half-life	9.5 hours
Protein Binding	97.8%
Volume of Distribution	Greater than 1000 L
Metabolism	Hydrolytic cleavage by esterases (Major) CYP3A4 (Minor)
Elimination	More than 90% of the dose eliminated via biliary/fecal excretion
Drug Interactions	P-glycoprotein (P-gp), CYP3A4 inducers
Dose Adjustments	**Baseline hepatic impairment**: • Child-Pugh Class A: Reduce dose to 100 mg twice daily. • Child-Pugh Class B or C: Nintedanib not recommended. **Treatment-induced hepatotoxicity**: • If AST or ALT increases to 3–5 times ULN, without signs of severe liver damage: Hold therapy or reduce dose to 100 mg twice daily. If values return to baseline, treatment may be restarted at a lower dose (100 mg twice daily), then increased to the full dose (150 mg twice daily). • If AST / ALT greater than three times ULN—with signs/symptoms of severe liver damage—or AST/ALT greater than five times ULN: Discontinue therapy
Monitoring Parameters	• LFTs for the first 3 months of treatment • GI effects for first 3 months of treatment • Bleeding events • Cardiovascular events • Pregnancy test before initiation for those of childbearing age

Table 1.
Nintedanib pharmacokinetic parameters and special considerations [4].

Arterial thromboembolic events have been noted in patients taking nintedanib, and caution should be exercised in those at high risk for cardiovascular events [4]. Basic pharmacokinetics and special population dosing can be found in **Table 1** [4].

6. Current therapy: pirfenidone

Pirfenidone (Esbriet®) is an oral synthetic pyridine derivative with anti-fibrotic and anti-inflammatory properties [7, 12, 23, 24]. Its anti-fibrotic effects arise from down-regulation of transforming growth factor (TGF) β and tumor necrosis factor (TNF) α [7, 23, 25]. It may inhibit fibroblast proliferation, expression of heat-shock protein 47, and collagen synthesis as well [7, 23–25]. Clinically, pirfenidone reduces worsening of FVC and may reduce risk of hospitalization [7, 23, 26]. Several studies like CAPACITY, ASCEND and RECAP have confirmed its long-term safety, efficacy, and favorable tolerability [7, 12].

Common side effects and clinical pharmacology can be found in **Table 2**. Most prevalent are gastrointestinal (GI) and skin-related adverse drug effects, which generally wane after the first 6 months and do not impact a patient's ability to continue and maintain a high-dose intensity [12]. Several side effects like fatigue, photosensitivity, and GI distress may require dose reductions [7, 12]. Fatigue, in particular, is observed

Bioavailability	**Unknown**
Half-Life	3.0 hours
Protein binding	Mean of 50–58% at concentrations of 1–10 μg/mL.
Volume of Distribution	Mean of 59–71 L following oral administration
Dosage and Administration	Recommend titration to 801 mg three times daily (2403 mg/day) with food
Metabolism and Excretion	Primarily metabolized in the liver and bio-transformed by CYP1A2 Roughly 80% dose excreted in urine as metabolite 5-carboxy-pirfenidone
Common side effects	Nausea, rash, dyspnea, diarrhea, fatigue, bronchitis, upper respiratory tract infections, dizziness, photosensitivity
Interactions	• CYP1A2 inhibitors (ciprofloxacin, fluvoxamine) may decrease metabolism and require dosing adjustments or discontinuation. • Grapefruit juice should be used with caution, though study results are inconsistent.
Warnings/Precautions	• Photosensitivity reactions may require dose adjustments. • Limit exposure to sunlight and sunlamps, use sunscreen (SPF ≥ 50) and protective clothing while taking. • GI side effects may be managed with temporary dose reduction, with gradual titration back to full dose. Taking after a full meal may help. • Mild-to-severe fatigue can be managed by dose modifications but may necessitate discontinuation. • Elevated liver enzymes (AST, ALT, bilirubin) occurred in trials and may require dose adjustments or discontinuation.
Monitoring Parameters	• Monitor liver function (AST, ALT, bilirubin) before initiating and each month after for six months, then every three months, or if the patient experiences symptoms of liver injury. • If ALT or AST exceeds 3–5 times ULN—with no symptoms—dose adjustments may be made. If 3–5 times ULN—accompanied with symptoms or hyperbilirubinemia—or > 5× ULN, discontinue permanently.

Bioavailability	Unknown
Special Populations	• Hepatic impairment: Monitor liver function monitored closely and potential for adverse reactions. Use contraindicated in those with severe hepatic dysfunction or end-stage liver disease • Renal impairment: Avoid severe kidney impairment (CrCl <30 mL/min) or dialysis. • Pregnant and nursing women: Not studied. It should be avoided during pregnancy and when nursing. • Geriatrics: No dose adjustments needed. • Pediatrics: Not studied.

Table 2.
Pharmacokinetic parameters and special considerations [7, 12, 27–29].

within the first few weeks of treatment and may substantially affect the quality of life. It may be difficult to distinguish from the disease itself, though it can be managed by dose modifications or even discontinuation [7, 12]. Several studies have examined the importance of taking pirfenidone with food [27, 28, 30, 31] Administration after meals slows absorption and may mitigate GI side effects [7, 12, 27, 28].

Updated practice guidelines recommend both nintedanib and pirfenidone [15]. Though both have been shown safe and effective, a lack of head-to-head trials makes it difficult to recommend one over the other [15]. The two agents have a different mechanism of action, making the prospect of combination therapy intriguing [12, 32]. However, when investigated, it was found that the combination led to greater photosensitivity and GI side effects [12, 32].

7. Acute exacerbations

Acute exacerbations (AE) are defined as an acute downturn in blood oxygenation, increased lung attenuation per computed tomography scan, and acute worsening of dyspnea [33]. Common causes include exposure to particulate matter (PM) ≥ 2.5 μm or crocin peptide released by *S. nepalensis*, bronchoscopy or lung biopsy, and inhalation of water repellant [33–36]. Sources of PM include tobacco smoke, candles, forest fires, and dust [33, 37]. The exact incidence of exacerbations is unknown but is estimated to vary between 5 and 20% [36, 38].

Since AE mortality rates range between 60 and 80% within a 90-day period, most care is strictly palliative in nature [39]. The two primary therapies include corticosteroids like prednisone and cytotoxic medications like cyclophosphamide. However, no proven benefit for these therapies has been demonstrated [40]. In addition, mechanical ventilation should not be employed due to poor outcomes [41]. Novel therapy involving administration of polymyxin B-immobilized fiber column (PMX-DHP), originally developed to manage sepsis by removing plasma endotoxins, has shown increased effectiveness [38, 42]. One limitation of its use is it can lower white blood cell counts via absorption of neutrophils [38, 39]. It remains most effective if administered within 3–7 days of AE onset [38, 39].

8. Clinical evidence for efficacy

The SENSCIS trial was a 52-week randomized, placebo-controlled, double-blind study examining the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD) with nintedanib [43, 44]. It was shown to decrease FVC

decline rate (mL/year) within the treatment group compared to placebo [3, 43]. An annual difference of −52.4 mL/year for nintedanib versus −93.3 mL/year for placebo was shown at 52 weeks [3, 43]. The INPULSIS trial, a 52-week, randomized, double-blind, phase 3 trial, showed a similar reduction in FVC decline rate with nintedanib versus placebo [3, 45]. TOMORROW, a 52-week, randomized, double-blind, placebo-controlled, phase 2 trial—alongside INPULSIS—showed a decrease in acute exacerbations with nintedanib compared to placebo [4, 45]. The INBUILD trial, a 52-week, randomized, double-blind, placebo-controlled, parallel-group trial, examined patients with progressive fibrosing interstitial lung diseases other than IPF [3, 46]. Treatment groups received nintedanib 150 mg twice daily or placebo [3, 46]. Reduction in FVC decline rate was uniform across the five subgroups [46, 47].

Three major trials have recently examined pirfenidone, including CAPACITY 004, CAPACITY 006, and ASCEND [4, 12]. The two CAPACITY trials were run side-by-side for 72 weeks [48, 49]. CAPACITY 004 showed a significant reduction in FVC decline with pirfenidone, though only a significant difference up to week 48 was seen in CAPACITY 006 [48, 49]. The ASCEND trial, a 52-week, phase 3 trial, found that patients with a predicted FVC > 50% at baseline received benefit from pirfenidone over 1 year, reducing the rate of decline by approximately 50% [4, 49]. ASCEND also analyzed 6 MW distance [49, 50]. There was a significant difference between baseline and week 52 with the two treatments, including a 27.5% reduction in the pirfenidone group [49, 50]. Pooled population data from all three trials showed a 48% reduced risk of death at 1 year compared to placebo [48, 49].

9. Comparison: nintedanib vs. pirfenidone

As mentioned above, both agents have been shown safe and effective in placebo-controlled, randomized trials [51–53]. Both may slow the FVC decline rate by almost 50% over 1 year [51]. The two treatments have also demonstrated remarkable efficacy in minimizing severe respiratory hospitalizations and acute exacerbations [51, 54]. Though both agents may reduce mortality, each cost over $100,000 annually [51, 55].

9.1 Mechanisms of action

Nintedanib has a unique mechanism of action compared to pirfenidone. It inhibits tyrosine kinase, an enzyme that targets growth factor (GF) pathway receptors like fibroblast GF, platelet-derived GF, and vascular endothelial GF [3, 4]. Elevated bleeding risk is seen in patients taking concomitant anticoagulation therapy [7, 15]. Patients should regularly monitor liver function and GI disturbances, including diarrhea [43, 46]. Conversely, pirfenidone inhibits collagen synthesis, downregulates TGF-β, tumor necrosis factor-α, and reduces fibroblast proliferation [7, 24, 26]. Side effects include abnormal liver function, anorexia, nausea, photosensitive rashes, and vomiting [56].

9.2 Dosing

Pirfenidone comes in a 267 mg capsule, initially dosed as one capsule three times daily the first week [56, 57]. During the second week, the dose can be increased to 534 mg three times daily, and—after two weeks—it can be fully titrated to 801 mg three times (2,403 mg or nine pills per day). It is recommended that each dose be taken after a full meal to minimize GI side effects like nausea, dizziness, and vomiting [56, 57]. Patients may be treated with nintedanib first-line if intolerability to pirfenidone occurs [56–58]. The maximum recommended dose is 150 mg twice daily [58, 59].

9.3 Research similarities and differences

In a 1-year evaluation of both medications, there was a slight decrease in FVC, especially in those with comorbidities, which may account for increases in hospitalization and all-cause mortality [60, 61]. In combined studies, pirfenidone displayed a slower rate of FVC decline than nintedanib, helping to explain increased hospitalizations and mortality with its use [60, 61].

9.4 Side effect profiles

Though pirfenidone is frequently associated with GI complications, diarrhea, and involuntary weight loss is more common with nintedanib [57, 58, 61]. Pirfenidone's side effects include dyspepsia, nausea, loss of appetite, phototoxic reactions, and difficulty concentrating. Sunscreen use is recommended when taking it. Conversely, nintedanib displays less nausea but greater transaminase elevations [57, 58, 61]. Pirfenidone is older and better studied more nintedanib, which may explain why its gastrointestinal and cognitive side effects are better understood [57, 58, 61]. Phototoxicity is generally absent with nintedanib [57, 61].

10. Therapeutic drawbacks

Though pirfenidone and nintedanib may slow disease progression, neither will cure IPF or markedly improve current symptoms [4, 62]. Symptom management, especially cough and dyspnea, is crucial to maintaining the quality of life [4, 63]. This is somewhat challenging given the lack of clinical evidence showing improvement in such symptoms and guideline focus on lung function [4, 63].

Both agents have noteworthy side effects. Nintedanib is most frequently associated with diarrhea, nausea, vomiting, and elevated liver enzymes [62]. By comparison, pirfenidone may cause nausea, diarrhea, dyspepsia, anorexia, and gastroesophageal reflux, as well as rash, upper respiratory infections, and fatigue [62, 64].

Another significant burden of IPF is cost [4, 65]. A recent systematic review estimated its annual cost in the United States at $20,000 per patient per year, about three times greater than the national health care resource use per capita [4, 65]. Hospitalizations and acute exacerbations are key drivers of this cost, with an average cost exceeding $16,000 for each IPF-related hospitalization [4, 66]. Due to their specialty drug and brand-only status, pirfenidone and nintedanib remain extremely expensive, with costs exceeding $10,000 per month per agent [4]. However, nintedanib is associated with fewer acute exacerbations and, consequently, decreased medical costs [4, 62, 67]. A recent comparison analysis from the United Kingdom found that the two drugs were comparable in estimated cost and health-related quality of life benefit [4, 68].

It is important to remember that the INBUILD trial was not powered to provide sufficient evidence for the use of nintedanib in rarer, specific fibrosing ILD [47]. However, it can be challenging to recruit patients with these rarer disease states. The fact that nintedanib reduced the rate of disease progression (i.e., FVC decline) in a wide range of progressive fibrosing ILD suggests utility in such populations [47].

11. Novel research/pipeline drugs

In recent decades, our understanding of IPF pathogenicity and management has improved significantly [15, 69]. However, many limitations, such as an inability

to translate experimental findings in animal models to human subjects, remain a challenge [69, 70]. Current therapies like nintedanib and pirfenidone are limited to pathways involved in reducing disease progression and physiological decline in those with mild-to-moderate impairment [15, 69]. Second-line treatments capable of improving functional capacity for such patients or benefiting the severely impaired are still needed [15, 70].

Other viable agents have been recently investigated [9]. Increased concentrations of endothelin receptors have been observed in IPF lung tissue [15]. As a result, several clinically significant endothelin receptor antagonists have been previously tested, including ambrisentan, a selective type-A antagonist, and bosentan and macitentan, type-A and type-B antagonists [71, 72]. Nonetheless, recent guidelines strongly discourage the use of ambrisentan given its risk of harm and lack of benefit, along with a conditional recommendation against the use of bosentan and macitentan [15, 73].

The phosphodiesterase-5 inhibitor sildenafil has been investigated due to its role in pulmonary vasodilation and improved gas exchange [15]. Past studies and analyses reported a slight but significant improvement in the degree of dyspnea and quality of life compared to placebo [15]. However, it has failed to demonstrate improvements in mortality, acute exacerbations, and adverse events [15]. Recent guidelines discourage its use, though it continues to be investigated [15, 73].

N-acetylcysteine (NAC), a precursor of the antioxidant glutathione, has also been examined for use in IPF [74]. A pooled analysis compared NAC monotherapy to placebo in IPF patients [15]. Ultimately, there was no significant difference in the rate of death or acute exacerbation, as well as no significant benefit in mortality, quality of life, or adverse outcomes [15]. Current guidelines strongly discourage its use in practice [15, 74].

A recent randomized clinical trial investigated imatinib mesylate (Gleevec®), a tyrosine kinase inhibitor. It showed a statistically significant increased risk of adverse events and no improvement in preventing disease progression or mortality [15, 74]. This distinct lack of benefit has led to its use being discouraged in IPF [15, 74].

Several active interventional and observational trials are currently underway. Recent novel studies suggest that genetic factors may play a crucial role in overall risk, disease progression, and therapeutic response [70, 75]. Future trials and drug development will likely focus more on genetic variation in IPF patients [70, 75].

12. Conclusions

IPF is a common ILD that is progressive and potentially fatal [4, 9]. It is characterized by decreased lung function stemming from abnormal fibrotic processes, ultimately leading to scarring tissue formation, diminished gas exchange, and reduced blood oxygenation [4, 7]. Though there is no known cause, it is more common in males and elderly patients and is associated with risk factors like smoking, environmental exposure, and multiple comorbidities [4, 9]. Due to insufficient understanding of its pathophysiological mechanisms, there are currently no therapies capable of preventing or reversing IPF [7, 9, 76]. Current management includes antifibrotic drugs like nintedanib (Ofev®) and pirfenidone (Esbriet®), which have been shown to slow lung deterioration [4, 7, 13]. Recent investigations examining nintedanib use in other ILDs with progressive phenotypes have shown favorable results, suggesting that such ILDs share similar mechanisms and may thus benefit from similar treatment [3, 77]. Imatinib mesylate (Gleevec®) is not recommended due to the increased risk of adverse events and no improvement in disease progression or mortality [17, 73]. Similarly, the use of ambrisentan (Letairis®)

is discouraged due to lack of effectiveness and increased risk of hospitalization [7]. Other IPF management strategies include smoking cessation, immunization, respiratory rehabilitation, oxygen supplementation, and management of comorbidities [4, 20]. More recent approaches have targeted biological processes linked to IPF, such as aging, oxidative stress, and epithelial-to-mesenchymal cell transition (EMT) [9, 76]. Ultimately, a better understanding of its underlying mechanisms is necessary to develop more effective treatments and reduce mortality [7, 9, 76].

Author details

Ladan Panahi[1,2*], George Udeani[1,2], Andrew Scott Tenpas[1,2], Theresa Ofili[1,2], Elizabeth Marie Aguilar[1,2], Sarah Burchard[1,2], Alexandra Ruth Ritenour[1,2], April Jacob Chennat[1,2], Nehal Ahmed[1,2], Chairat Atphaisit[1,2], Crystal Chi[1,2], Jesus Cruz III [1,2], Monica D. Deleon[1,2], Samantha Lee[1,2], Zack Mayo[1,2], Mackenzie Mcbeth[1,2], Mariel Morales[1,2], Jennifer N. Nwosu[1,2], Kelly Palacios[1,2], Jaycob M. Pena[1,2] and Nitza Vara[1,2]

1 Department of Pharmacy Practice, Texas A&M Rangel College of Pharmacy, Kingsville, Texas, USA

2 Department of Pharmacy Practice, Texas A&M Rangel College of Pharmacy, College Station, Texas, USA

*Address all correspondence to: panahi@tamu.edu

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