Published in final edited form as:

Ann Med. 2015 March ; 47(2): 100–105. doi:10.3109/07853890.2014.991751.

Pharmacologic Therapies for Idiopathic Pulmonary Fibrosis, Past and Future

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a severe, progressive fibrotic disease of the lung of unknown etiology that affects approximately 150,000 patients in the United States. It carries a median survival of two to three years, but clinical course can vary markedly from patient to patient. There has been no established treatment for IPF, but recent advances in coordinated clinical trials through groups such as IPFnet and academia-industry partnerships have allowed this relatively rare disease to be studied in much greater depth. Historically, the default therapy for IPF was a combination of prednisone, N-acetylcysteine, and azathioprine, but recent trials have shown that this regimen actually increases mortality. An enormous body of work in recent years, spanning the bench to the bedside, has radically altered our understanding of the molecular mechanisms underlying IPF. Newer modalities, particularly those involving monoclonal antibodies targeted at specific pathways known to contribute to the fibrotic process, have generated a great deal of excitement in the field, and recent clinical trials on therapies such as pirfenidone and nintedanib herald a new era in targeted IPF therapies.

Keywords

idiopathic pulmonary fibrosis; N-acetylcysteine; nintedanib; pirfenidone; prednisone

Introduction

Pulmonary fibrosis is the final common pathway for many diffuse parenchymal diseases of the lung. Idiopathic pulmonary fibrosis (IPF) is a diffuse fibrotic process of the lung of unknown etiology that carries with it a median survival of two to three years after diagnosis (1),(2). Establishing exact incidence and prevalence of the disease has been difficult, owing to recent changes to diagnostic criteria (3), but it is now recognized as the most common of the idiopathic interstitial pneumonias, affecting approximately 150,000 people in the US (4), (5), and accounting for around 30% of lung transplants performed worldwide (6). Clinically, it is characterized by progressive dyspnea and dry cough. Examination often reveals early

inspiratory crackles in the lower lung fields and associated clubbing (7). Signs of right heart failure may be present in advanced disease.

American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines for the treatment of IPF published in 2000 categorized treatment types into corticosteroids, immunosuppressive/cytotoxic agents (e.g. azathioprine), and antifibrotic agents (e.g. colchicine) (8). Treatment of IPF had historically focused on steroids and other immunosuppressive medications in strategies designed to disrupt the inflammatory cascade, of which fibrosis was hypothesized to be the end result (9). When such strategies proved ineffectual in practice, debate ensued as to the role of inflammation in the pathogenesis of IPF. Consensus currently leans toward aberrant wound healing rather than a disorder of inflammation. Importantly, such hypotheses can be tested in a more robust clinical environment, thanks to stricter diagnostic criteria as outlined in recent guidelines (3) and the development of coordinated networks such as IPFnet that allowed for the performance of controlled clinical trials.

Clinical trials have been hampered by a highly variable progression of disease (10) characterized by rapid decline, periods of relative stability punctuated by periods of acute decline, or slow progression. Given the fact that a decline in forced vital capacity (FVC) has been repeatedly shown to predict mortality, it is frequently chosen as the primary endpoint in clinical trials. However, many have argued that mortality would be a more relevant endpoint (11), but the numbers required would likely be prohibitive. The result has been a multitude of clinical endpoints that has made comparing clinical efficacy quite difficult. Nevertheless, over the last ten years there has been a remarkable proliferation in appropriately-designed clinical trials of potential treatment options for IPF. Although no single therapy has yet emerged as capable of halting the progression of disease, recent trials of pirfenidone and nintedanib have generated more excitement in the field than ever before. This review will provide a historical background for the treatment of IPF and detail some of the newer therapies under investigation.

Prednisone and Azathioprine

Historically, treatment of IPF has focused on the use of corticosteroids due to their anti-inflammatory effects. Data supporting this approach was weak, however, and a 2004 Cochrane review of the evidence found no studies meeting the criteria for meta-analysis and no support for their use (12). The review was updated with a similar conclusion in 2010 (13). Immunomodulating agents have also been used for the treatment of IPF, also with little data supporting their use. That said, a study evaluating the use of azathioprine and prednisone versus prednisone and placebo found a trend toward improvement in resting oxygen saturation and a slight improvement in survival (14). A more definitive answer to the question of steroids and immunomodulating agents was provided by PANTHER-IPF, a multicenter randomized controlled trial, launched by the NIH to evaluate the use of prednisone, azathioprine, and N-acetylcysteine (NAC).

PANTHER-IPF was a randomized, double-blind, placebo-controlled trial in which patients with IPF and mild-to-moderate impairment in lung function were randomized to prednisone,

azathioprine, and NAC (combination therapy); NAC alone; or placebo. The primary outcome assessed in the study was the longitudinal measurement of FVC over a 60-week treatment period. A planned interim analysis after a mean follow-up of 32 weeks found an increased rate of death in the combination therapy group when compared to the placebo group (8 versus 1, $p = 0.01$), and hospitalization (23 versus 7, $p < 0.001$). Given these data, the independent data and safety monitoring board recommended termination of the combination therapy group (15) with continuation of the NAC and placebo arms (discussed below). Since the publication of the study, it has been noted that the excess mortality and hospitalizations occurred early in the trial, roughly coinciding with the period of higher dose prednisone, tapered over the first 4-6 months to a low daily dose, suggesting that the highest toxicity may have been due to high dose corticosteroids, rather than the azathioprine and low dose prednisone. Nevertheless, the increased mortality and hospitalization rate associated with prednisone and azathioprine means that this combination of agents should no longer be used in IPF. Further, the fact that prednisone and azathioprine are now known to increase mortality in IPF underscores the importance of obtaining a correct diagnosis for a patient's fibrotic lung disease, since other diagnoses such as fibrotic hypersensitivity pneumonitis and connective tissue disease-associated interstitial lung disease, which may mimic IPF, may respond more favorably to immunosuppression.

N-acetylcysteine

N-Acetylcysteine (NAC), a mucolytic agent, has been prescribed as a treatment for chronic bronchitis. Its antioxidant properties have also made it an attractive option for the treatment of patients with IPF, since the disease process has been associated with excessive oxidative stress (16),(17). NAC augments the synthesis of glutathione *in vivo* (18), replenishing stores and restoring the epithelial cell antioxidant defense mechanism. Importantly, glutathione levels are also reduced in the lungs of patients with IPF (19). In the clinical arena, the IFIGENIA trial, a multicenter, randomized, double-blind, placebo-controlled trial examined outcomes in patients who received either NAC or placebo in addition to prednisone and azathioprine. The trial demonstrated a reduced rate of decline in FVC and DLCO in patients treated with NAC, but no improvement in survival at one year (20). The lack of a proper placebo arm drew some criticism (21), but concerns over the study design were addressed in the NAC versus placebo arm of PANTHER-IPF, a placebo-controlled multicenter study (22). Although NAC was not effective in slowing down the rate of IPF progression, at least as measured by the primary outcome of FVC change at 60 weeks, it was found to benefit mental well-being when compared to placebo, although the mechanisms of such a benefit are as yet unclear. Given the results of this trial, though, the use of NAC cannot be recommended as treatment for IPF at the present time.

Interferon-gamma

The imbalance between profibrotic and antifibrotic cytokines in the lungs of patients with IPF led to the use of interferon gamma (IFN- γ) in clinical trials. IFN- γ has been shown to suppress fibroblast proliferation and down regulate transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), and various other profibrotic interleukins *in vitro* and *in vivo* studies (23). Initial clinical trials showed a trend toward decreased mortality (24)

but the INSPIRE study, a larger prospective trial, failed to show any survival benefit with subcutaneous IFN- γ treatment (11).

In 2012, a small clinical trial performed to evaluate the safety of inhaled IFN- γ found that patients in the treatment group showed a reversal in the slope of decline of their TLC and DLCO (25). FVC and 6MWT showed minimal change. Larger studies are needed to better determine the potential benefit of this therapy.

Endothelin Receptor Antagonists

Experimental work in the early 1990s demonstrated that Endothelin-1 (ET-1) expression is upregulated in IPF (26). It is thought to contribute to neovascularization (27), collagen synthesis (28), and fibroblast proliferation (29),(30). The endothelin receptor antagonist bosentan was found to attenuate bleomycin-induced fibrosis in animal models (31). However, no significant difference between the bosentan and placebo arms in the primary end point of six minute walk distance (6MWD) was seen in patients with IPF without evidence of severe pulmonary hypertension (32). More recent data in patients with IPF found no improvement in primary endpoint (progression-free survival) when compared to placebo (33). Two other endothelin receptor antagonists, ambrisentan and macitentan, were evaluated in ARTEMIS-IPF and MUSIC, respectively. ARTEMIS-IPF, a phase III trial, was halted due to a lack of efficacy. In addition, patients on the study drug demonstrated more progression and hospitalization than patients on placebo. MUSIC, a phase II trial, did not meet its primary endpoint of improvement in FVC and there appear to be no plans for further trials.

Sildenafil

A substantial proportion of patients with IPF have been shown to develop pulmonary hypertension over time (34). Sildenafil, an oral phosphodiesterase-5 inhibitor, is used in the treatment of pulmonary arterial hypertension. Its utility in IPF is unclear, but patients with IPF and concomitant pulmonary hypertension are known to have an increased mortality rate (35). Studies evaluating the use of sildenafil in this setting has been shown to improve pulmonary hemodynamics by blocking PDE-5 in well-ventilated areas of the lung with minimal increase in shunting (36),(37), but a subsequent randomized controlled trial did not meet its primary endpoint of 20% improvement in 6MWD at 12 weeks. Other metrics, including dyspnea, oxygen tension, and DLCO, all showed statistically significant improvements (38). In addition, it is important to note that the study did not analyze the subset of patients who have pulmonary hypertension due to IPF, and it is unclear if those patients would indeed benefit from the drug.

Tyrosine Kinase and Serine-Threonine Kinase Inhibitors

Various protein kinase inhibitors have been developed for the treatment of malignancies through targeted action against particular cells. Protein kinases have been linked to the process of fibrogenesis through the action of growth factors such as TGF- β (39). Tyrosine kinase inhibitors (TKIs) have been used in the treatment of IPF to specifically inhibit the action of fibroblasts, effector cells integral to the progression of IPF.

Platelet derived growth factor (PDGF) has been shown to induce procollagen production by fibroblasts (40). Imatinib mesylate, a tyrosine kinase inhibitor that acts on PDGF, Bcr-Abl, and c-kit, failed to show any improvement in lung function or progression free survival (41).

BIBF1120 (now known as nintedanib) on the other hand, acts on the vascular endothelial growth factor (VEGF) receptor, the fibroblast growth factor (FGF) receptor, and the PDGF receptor. In TOMORROW, a twelve-month phase II trial, four oral doses of BIBF1120 were compared to placebo in patients with IPF (42). The primary end point was the rate of decline in FVC. Randomizing over 400 patients to receive one of four doses, the study found that those taking the higher dose of 150 mg twice a day declined by 0.06 liters per year as compared to 0.19 liters per year in the placebo group (a benefit of 68.4%, $p = 0.06$). The same dose also resulted in a significantly lower incidence of acute exacerbations ($p = 0.02$) and an improved quality of life (as measured by the St George's Respiratory questionnaire) versus placebo ($p = .007$). The most frequently observed side effects included gastrointestinal symptoms and increases in liver transaminases. Such promising data encouraged the pursuit of phase III trials, which were published in May 2014. INPULSIS-1 and INPULSIS-2 were both one year-long randomized, placebo-controlled trials examining the efficacy of 150 mg twice daily. The primary endpoint was the annual rate of decline in FVC (43). In both studies, nintedanib significantly reduced the rate of decline in FVC by approximately half. The adjusted annual rate of change in the nintedanib group was -114.7 mL and -239.9 mL in the placebo group ($p < 0.001$) in INPULSIS-1, and -113.6 mL in the nintedanib group and -207.3 mL in the placebo group in INPULSIS 2. Diarrhea was the most common adverse event. Based on these results, the manufacturer approached the FDA; the drug was approved for therapeutic use in October 2014.

Pirfenidone

Pirfenidone is an oral pyridine derivative observed to have a range of anti-fibrotic actions, although its exact molecular mechanism is as yet unclear (44). In murine models, it has been shown to reduce levels of TGF- β , FGF, and PDGF, as well as levels of procollagens I and III (45),(46),(47). An early clinical trial demonstrated its efficacy in patients with advanced disease, the majority of whom experienced a slower decline in lung function and reduction in corticosteroid dose (48). It was then studied in several randomized placebo-controlled multicenter trials (49),(50),(51). In CAPACITY 2, 174 patients were assigned to 2403 mg/day pirfenidone, 87 patients were randomized to pirfenidone 1197 mg/day, and 173 patients were randomized to placebo. The primary endpoint, decline in FVC at 72 weeks, was reduced from -12.4% to -8.0% in the higher dose pirfenidone group versus placebo, $p = .001$. In CAPACITY 1, a similarly designed study with the same primary endpoint, patients were randomized in a 1:1 fashion, 171 patients to 2403 mg/day pirfenidone and 173 to placebo. No significant difference in FVC decline between pirfenidone and placebo-treated patients was observed at the pre-specified time point of 72 weeks. Side effects included photosensitivity, gastrointestinal symptoms, and liver function abnormalities. Based on these data, pirfenidone became the first therapy for IPF to be licensed initially in Japan and then in Europe, though the FDA declined approval for its use in the United States, based on the negative results of the CAPACITY 1 trial. In order to obtain enough data for approval by the FDA, the manufacturer launched the ASCEND trial, the results of which

were published in May 2014. ASCEND was a randomized placebo-controlled trial of 555 patients. The primary endpoint was the change in FVC from baseline to week 52. Pirfenidone treatment was associated with a significant reduction in FVC decline at one year and improvement in progression-free survival (52). No significant difference in dyspnea scores, mortality from IPF, or all-cause mortality was observed. However, when data from ASCEND and CAPACITY were pooled, the results suggested a reduction in all-cause and IPF-related mortality. Based on those results, the manufacturer approached the FDA again and the drug was approved for therapeutic use in the United States in October 2014. Of note, a recent study on the long-term safety profile of pirfenidone showed that the drug is generally well tolerated, with gastrointestinal and skin-related side effects being the most common, but rarely leading to treatment discontinuation (53). Another paper discussing the management of patients on pirfenidone makes specific recommendations regarding the timing of drug doses to minimize adverse events as much as possible (54).

Angiotensin Converting Enzyme Inhibitors and Receptor Blockers

Angiotensin has been shown to induce epithelial apoptosis as well as procollagen synthesis by human lung fibroblasts, at least partially mediated through TGF- β signaling (55). Myofibroblasts in patients with IPF have also been demonstrated to express more angiotensin and TGF- β than control fibroblasts (56). ACE inhibitors (57) and losartan (55) have been shown to attenuate laboratory models of pulmonary fibrosis and have been associated with a reduction in epithelial cell apoptosis and TGF- β expression (58). Angiotensin II levels are also increased in humans with IPF, specifically at sites of epithelial apoptosis and fibrotic foci (59). On the strength of the experimental evidence, trials to evaluate the clinical efficacy of losartan in IPF are underway (NCT00879879). However, a large retrospective study of patients with IPF who were on a statin, ACE inhibitor, or both found no survival benefit using either drug or the combination (60).

Anticoagulation

The coagulation cascade has been linked to the fibroproliferative response to lung injury (61) through the elevated thrombin levels seen in the lavage fluid of patients with fibrotic lung disease (62). Further, Factor X has been found in intra-alveolar space of patients with IPF. Anticoagulants have been shown to attenuate fibrosis in experimental animal models (63),(64),(65) and a non-blinded prospective randomized trial of patients receiving prednisolone and anticoagulation versus prednisolone alone showed increased three year survival and reduced mortality during exacerbations (66). Concerns over the unblinded nature of the trial led to a double-blinded randomized placebo-controlled study, AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis, which was recently stopped after an interim analysis showed a lack of efficacy as well as an increased risk of mortality (67).

Tumor Necrosis Factor Inhibitors

Evidence that levels of TNF- α are increased in the lungs of patients with lung fibrosis has led to interest in TNF- α as a target in IPF (68),(69),(70). Laboratory studies have found that TNF- α blockade attenuates fibrosis in bleomycin models (71),(72),(73),(74) and more recent

studies have linked TNF- α to the response to lung injury through the adaptive immune system (75). A randomized, double-blinded, placebo-controlled trial of Etanercept, a TNF- α receptor antagonist, showed no significant differences in the change from baseline at 48 weeks in corrected DLCO, FVC, and A-a gradient (76) in the treatment group.

Thalidomide

Thalidomide has been used as a treatment for many conditions, notably multiple myeloma, despite its well-known teratogenic effects. It has been shown to attenuate lung fibrosis in murine models (77), possibly owing to its immunomodulatory (78) or anti-angiogenic properties (79). A randomized trial published in 2013 showed a significant improvement in cough and respiratory quality of life (80) and an open label study is being conducted to evaluate the safety and efficacy of thalidomide in the treatment of patients with IPF (NCT00162760).

Inhaled carbon monoxide

Carbon monoxide is a biologically active molecule and is a product of heme oxygenase activity in the body. CO has been shown to have antifibrotic activity in animal models (81). Matrix metalloproteinase -7 (MMP-7) is overexpressed in the lung in IPF. A phase II trial designed to investigate whether inhaled CO leads to a decrease in blood levels of matrix metalloproteinase 7, an enzyme that has been shown to reflect the alveolar microenvironment is currently underway (NCT01214187).

Monoclonal antibodies under investigation

LOXL2

Lysyl oxidase-2 (LOXL2), an enzyme that plays an essential role in the maintenance of the microenvironment in fibrotic diseases by catalyzing the crosslinking of collagen, has been found to be upregulated in IPF (82). A monoclonal antibody to LOXL2 known as simutuzumab (GS-6624) is currently under investigation for treatment of IPF in phase II trials (NCT01769196)

CTGF

Connective tissue growth factor (CTGF) is known to modulate several signaling pathways including cell adhesion and migration, angiogenesis, and extracellular matrix deposition and has emerged as a potential therapeutic target in IPF. Its expression is elevated in the fibroblasts of patients with IPF (83) and has been shown in murine models to be necessary and sufficient for TGF- β mediated fibrosis in the lung (84). A neutralizing antibody to CTGF, FG-3019, was found to be safe in a phase II clinical trial (85). Studies are ongoing to determine its potential use as a treatment in IPF.

CCL2

Chemokine (C-C motif) ligand 2 (CCL2), a monocyte chemoattractant that has been associated with IPF, also promotes fibrosis through the TGF- β pathway by mediating the signal of the Th2 cytokine IL-13 (83). An anti-CCL2 antibody, CNTO888, has been

investigated as a potential therapeutic target in IPF (86), but the data have not yet been fully published.

IL-13

Levels of IL-13 are elevated in the bronchoalveolar lavage fluid of patients with IPF (83). It has previously been found to promote fibroblast collagen production and fibroblast to myofibroblast differentiation. IL-13 has also been implicated in abnormal epithelial crosstalk in IPF. These preclinical findings have made IL-13 an attractive therapeutic target for IPF. Three different IL-13 antibodies are currently under investigation: tralokinumab (NCT01629667), lebrikizumab (NCT01872689), and SAR156597, a dual IL-13/IL-4 antibody (NCT01529853), all currently in phase II trials.

CC-930

C-jun N-terminal kinase, a MAP kinase, has been found at increased levels in activated form in epithelial and endothelial cells from the lung tissue of patients with IPF (87). That observation led to the hypothesis that MAP kinases may be involved in the regulation of lung inflammation and injury, but trials of CC-930, an orally active JNK inhibitor were terminated by the manufacturer, who cited concerns over the risk/benefit ratio of the drug (NCT01203943).

TGF- β 1 pathway

TGF- β 1 promotes fibroblast to myofibroblast differentiation and has been shown to be sufficient to drive progressive fibrosis in mice (88). Given that, and despite the fact that TGF- β 1 may have positive effects as a tumor suppressant, the inhibition of TGF- β 1 and its signaling pathway have long been an attractive therapeutic target in IPF. GC1008, an antibody that neutralizes all three TGF- β isoforms (all of which have been shown to stimulate lung fibroblast pro-collagen production), has successfully completed phase I testing (NCT00125385). Also targeting the TGF- β 1 pathway is the humanized monoclonal antibody STX-100, which specifically targets integrin α v β 6. This integrin has been found in low concentrations in normal epithelial tissues and is upregulated in injured epithelia, including in IPF. Its role in activating the TGF- β 1 pathway in target areas offers the hope that blocking it may prevent TGF- β 1-mediated fibrosis without blocking its beneficial effects elsewhere in the body (89). Phase I trials have been completed and phase II trials are currently recruiting (NCT01371305).

Summary

A stronger understanding of the molecular mechanisms underlying IPF has led to the development of novel therapies that address the various pathways involved in the disease process. The recent approval by the FDA of pirfenidone and nintedanib heralds a new era of targeted molecular therapy and holds out hope for patients with this rare disease.

Acknowledgements/Disclosures

BSS is supported by a training grant from the National Institutes of Health (T32 HL 076118-09). ER is supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation

Trust and Imperial College London and has received speaker's fees from AstraZeneca, Intermune and Takeda. SV has received consultancy fees from Intermune.

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Key Messages

1. Idiopathic pulmonary fibrosis (IPF) should not be treated with the combination of prednisone, azathioprine, and N-acetylcysteine.
2. An improved understanding of the molecular basis of IPF has led to targeted treatment options, and coordinated clinical networks are allowing for the study of these new therapeutics in larger and more sophisticated clinical trials.
3. Promising clinical results for pirfenidone and nintedanib herald a new era of therapies for patients with idiopathic pulmonary fibrosis.