REVIEW ARTICLE

A review of current and novel therapies for idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressively fibrotic interstitial lung disease that is associated with a median survival of 2-3 years from initial diagnosis. To date, there is no treatment approved for IPF in the United States, and only one pharmacological agent has been approved outside of the United States. Nevertheless, research over the past 10 years has provided us with a wealth of information on its histopathology, diagnostic work-up, and a greater understanding of its pathophysiology. Specifically, IPF is no longer thought to be a predominantly pro-inflammatory disorder. Rather, the fibrosis in IPF is increasingly understood to be the result of a fibroproliferative and aberrant wound healing cascade. The development of therapeutic targets has shifted in accord with this paradigm change. This review highlights the current understanding of IPF, and the recent as well as novel therapeutics being explored in clinical trials for the treatment of this devastating disease.

KEY WORDS

Idiopathic pulmonary fibrosis/drug therapy; idiopathic pulmonary fibrosis/pathology; molecular targeted therapy; clinical trials

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common and predominantly lethal form of the idiopathic interstitial pneumonias, with an associated median survival of only 2 to 3 years (1). The etiology of this chronic and progressive fibrotic lung disease is by definition unknown, although potential risk factors such as cigarette smoking and other environmental exposures have been described (1). While the diagnosis of IPF remains one of exclusion, its definition and the approach to its detection have evolved over the past decade (1,2). There has been a shift in the understanding of the pathophysiology of IPF from one of a chronic inflammatory state to one of abnormal wound healing. Aberrant fibroblastic proliferation and accumulation of extracellular matrix (ECM) proteins such as collagen have been the focus of more recent therapeutic experiments for IPF (3). This review highlights the current understanding of IPF, and the therapeutic clinical trials recently completed or underway for this devastating disease.

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Epidemiology

Incidence and prevalence

The incidence and prevalence of IPF have been difficult to define as the diagnostic criteria for this disease have changed over the years (4). A United-States population-based study published in 1994, reported the incidence of IPF to be 10.7 cases per 100,000 per year for men and 7.4 cases per 100,000 per year for women (5). In a study published in 2006 based on a United States healthcare claims database, the prevalence of IPF was between 14-42.7 per 100,000, depending on whether narrow or broad case-finding criteria was used (6). Most recently, in May 2012, a systematic survey of literature estimated the prevalence of IPF in the European Union to be 26 per 100,000. The findings of various studies on the incidence of IPF are summarized in Table 1.

IPF represents the most common cause of death from progressive lung disease. Retrospective studies suggest that the median survival after diagnosis of IPF is 2-3 years, however, the course of IPF is variable, with some patients experiencing long periods of stability while others have frequent exacerbations or a rapid decline (1,11,12).

Table 1. Incidence of IPF.

Country or region of study (data source)	Incidence per 100,000	Authors
United States (healthcare claims database)	6.8-16.3	Raghu *et al*. 2006 (6)
United Kingdom (primary care database including diagnostic and prescribing data)	7.44	Navaratnam *et al*. 2011 (7)
Greece (survey of pneumonology departments)	3.38	Karakastani *et al*. 2009 (8)
Finland (hospital diagnostic coding databases)	16-18	Hodgson *et al*. 2002 (9)
European Union (review of medical literature)	26	Orphanet 2012 (10)

Permission has been obtained from John Wiley and Sons for reuse of figure Table 1.

Age

IPF is more commonly seen in patients between 40 to 70 years of age (13). The incidence of this disease increases with age, and approximately two-thirds of those with IPF are older than 60, with a mean age at diagnosis of 66 years (7,13). The risk of death as a result of IPF also increases with age (1,7), with a hazard ratio (HR) of 0.25 for patients younger than 50 years (14) and a longer median survival amongst those younger than 50 (116.4 months compared to 62.8 months) (15). However, it has been suggested that this finding (i.e., younger age conferring longer survival from the time of IPF diagnosis) may be due to the inclusion of subjects with other types of interstitial pneumonias or varying definitions of disease onset in the older studies reporting these results (16). Nevertheless, age-related changes affecting cell regulation are likely important in the development of IPF (17).

Sex and race

IPF occurs more commonly in men than in women and may also progress faster and result in worse survival in men (18-20). Differences in disease progression, however, do not completely explain better survival in women (18). The IPF mortality rate in the United States was found to be 61.2 deaths per 1,000,000 in men and 54.5 per 1,000,000 in women (21), nevertheless, the death rate in women is increasing at a faster rate than in men (21). Age-adjusted mortality has been found to be greater among whites than blacks and is increasing at a higher rate among whites when compared to other racial and ethnic groups (21). Age-adjusted mortality among Hispanics has also been found to be lower than white non-Hispanics (21). Race and ethnicity may thus play a role in the susceptibility to IPF.

Diagnosis

The diagnosis of IPF requires the consideration of a detailed clinical history of the patient, a thorough investigation and exclusion of known causes of interstitial lung disease (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity), radiographic concordance and, in certain cases, pathological confirmation by surgical lung biopsy (1).

The histopathological criteria for IPF are those of usual interstitial pneumonia (UIP). Within the lungs, UIP is a temporally and geographically heterogeneous mixture of fibrosis, scarring and honeycombing along with areas of less affected or unaffected parenchyma. The subpleural and paraseptal parenchyma are more severely affected (1,2). It is important to note that UIP is not unique to IPF, and that other interstitial lung diseases such as chronic hypersensitivity pneumonitis, some connective tissue diseases, and pneumoconioses such as asbestosis may reveal this histopathology as well (1,2).

A specific UIP pattern has been described with respect to high-resolution computerized tomography (HRCT) of the chest (1). This entails the presence of reticular opacities with a subpleural basal predominance, honeycombing with or without traction bronchiectasis, and the absence of features that coincide more with other known forms of interstitial lung disease such as ground glass opacities, mosaic attenuations, and cystic disease (1). Overall, the positive predictive value of an HRCT diagnosis of UIP ranges from 90-100% (1). A consensus has evolved that surgical biopsy is usually not required when patients have clinical and radiographic features that fit the accepted UIP pattern (22).

In summary, the diagnosis of IPF requires: (I) exclusion of other known causes of interstitial lung disease, (II) the presence of an UIP pattern on HRCT in patients not subjected to surgical lung biopsy, and (III) specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy (1).

Pathogenesis

Great advances have been made in the understanding of the

pathogenesis of this disease and with this, a hope of a more targeted approach in therapy has emerged. Borchers *et al*. describe the research efforts that have focused on better understanding the reasons for an increased presence of fibroblasts in IPF lungs (23). The prevailing hypothesis is that UIP histology stems from repeated epithelial injury leading to the activation of alveolar epithelial cells (AECs) (23). These AECs then attract and activate fibroblasts and induce fibroblast proliferation and differentiation into myofibroblasts. Improper re-epithelialization leads to continued accumulation of myofibroblasts and their production of an excess of extracellular matrix. A possible role of humoral immunity, and autoimmune reaction, as well as genetic influences gleaned from those with familial IPF have also been described (23).

In light of these advances, IPF is not currently viewed as a purely inflammatory disorder. Rather, UIP is seen as a state of abnormal wound healing (11,24), "with progressive extracellular matrix accumulation, decreased fibroblast-myofibroblast cell death, continuous epithelial cell apoptosis, and abnormal re-epithelialization."(11) It is likely for this reason that broad anti-inflammatory and immunosuppressive therapies have not been able to alter this progressively fatal disease. Selman and colleagues propose that future treatments for IPF must be directed at crippling the fibroproliferative response and promoting normal alveolar re-epitheliazation (11).

The role of an inflammatory response in the pathogenesis IPF remains, however, and has been highlighted by recent work with murine lung injury models. These data support the pathogenic role of an early inflammatory response involving danger signals in the form of uric acid production; with an attenuation in observed fibrosis following the administration of agents to reduce tissue uric acid levels (25). Elevated uric acid levels have also been observed in human IPF lungs as compared to non-fibrotic lungs (26). While the expression of genes associated with acute inflammatory pathways has not been found to be increased in IPF, several genes encoding for chemokines and cytokines are upregulated (27). Therefore, consideration of more finely tuned anti-inflammatory therapies such as the selective modulation of key inflammatory pathways has also been proposed (28).

A history of treatment strategies

Unsuccessful treatments to date

Anti-inflammatory/immunomodulatory agents

Corticosteroid monotherapy

Corticosteroids such as prednisone suppress cellular and humoral immunity, reducing the levels of pro-inflammatory molecules. As IPF was initially considered a primarily inflammatory disease, broad immunosuppression was considered as a potential therapy. A 2003 Cochrane database analysis that was assessed as up-to-date in 2008, concluded that there have been no adequate randomized controlled trials to assess the efficacy of corticosteroid monotherapy in IPF (29). Furthermore, the use of chronic corticosteroids has been shown to be associated with a significant number of co-morbidities (30) and controlled cohort studies have revealed no survival benefit among those treated with corticosteroids (31). Given the advances in our understanding of the pathophysiology of this disease, trials with corticosteroid monotherapy are no longer justified and their sole use in IPF is not recommended in the more recently published consensus statement (1).

Azathioprine

Azathioprine, an immunosuppressant that blocks the function of proliferating cells such as T cells and B cells and also decreases the number of circulating monocytes and granulocytes, has long been considered as potential therapy for IPF. The use of azathioprine plus prednisone was associated with an improvement in lung volumes and gas exchange in a small retrospective study in 1978 (32). When analyzed prospectively in a randomized double-blind controlled study (azathioprine/prednisone versus prednisone/placebo), there was a trend towards survival benefit in the treatment arm, though it did not meet statistical significance (33). Interpretation of these studies is made difficult as they include the use of older, less defined diagnostic criteria for IPF that have since changed (34). Azathioprine in combination with prednisone was more recently prospectively evaluated for IPF in a randomized, placebo controlled, double-blind trial (clinicaltrials.gov identifier NCT00518310). The results of this latter study have not yet been published and the use of azathioprine along with corticosteroids is not currently recommended.

Cyclophosphamide

Cyclophosphamide, a cytotoxic chemotherapeutic agent, has been evaluated as a therapy for IPF in combination with prednisone. While no prospective, randomized trials of this drug combination exists, two retrospective reports are available. In one study of 82 patients, a survival advantage was observed among those treated with prednisone/cyclophosphamide versus those with prednisone monotherapy, however, this applied only to those with less severe disease as measured by forced vital capacity (FVC ≥70%) (35). Collard *et al*. reviewed the use of corticosteroids plus cyclophosphamide compared to no pharmacotherapy in a larger (n=164) retrospective controlled study and found no significant difference in mortality between the two (36). Therefore, current recommendations advise against the treatment of IPF with a combination of corticosteroids and immunomodulator

therapy (1).

Everolimus

Everolimus, a derivative of rapamycin, is a macrocyclic proliferation signal inhibitor with immunosuppressive and anti-fibroproliferative properties, currently used as immunosuppressant to prevent transplant rejection (37). By arresting the cell cycle at the G1 to S phase, everolimus inhibits growth factor-dependent proliferation of hematopoietic and non-hematopoietic cells such as vascular smooth muscle cells and human adult lung fibroblasts (37). Everolimus has been observed to attenuate bleomycin-induced pulmonary fibrosis in the rat model. Its safety and efficacy in the management of IPF was recently assessed in a randomized, placebo-controlled 3-year study of 89 patients (Australian New Zealand Clinical Trials Registry number ANZCTR 12605000599673). Everolimus was associated with a more rapid disease progression (mean time to disease progression defined as deterioration in pulmonary function =180 days) when compared to the placebo group (mean =450 days to disease progression) (37). The authors note that a higher dose of everolimus (8 mg) was used than that usually administered in solid organ transplantation. Nearly half (48%) of patients in the treatment arm were unable to tolerate this initial dose due to side-effects, and 23% of patients in the everolimus group discontinued the drug for this reason (37). While the fact that 68% of subjects randomized to everolimus overall had stopped the study drug by 12 months compared with only 12% of subjects randomized to placebo (38) makes interpretation of results difficult, it is concluded that everolimus, despite its immunosuppressive and anti-fibroproliferative properties, has not proven effective in the management of IPF, and may in fact be harmful.

Anticoagulants and the coagulation cascade

Repetitive and widespread injury to the alveolar epithelium is considered to be the pathogenic force behind IPF. Wound repair involves the activation of the coagulation cascade, inflammatory cell recruitment and the formation of a provisional matrix to prevent blood loss (39). In the fibrotic lung, tissue factor (40) and thrombin (41) are highly expressed, while the activation of protein C is decreased, resulting in an increase in procoagulant activity in the alveolar spaces (42) as well as abnormal collagen turnover within the alveoli (43).

Prophylactic or therapeutically administered anticoagulants are effective in ameliorating fibrosis in animal bleomycin models (44,45). The use of anticoagulants has therefore been evaluated among patients with IPF.

Warfarin/heparin/prednisolone

Kubo and colleagues published a non-blinded randomized trial of 56 patients with IPF in Japan (46). Patients were assigned to receive prednisolone only or prednisolone plus anticoagulant therapy (oral warfarin or low-molecular weight heparin). They reported significantly increased mortality in the non-anticoagulant group compared to the anticoagulant group (HR=2.9) after 3 years of therapy. Mean plasma levels of D-dimer were significantly higher in patients who died from AE (3.3 *vs*. 0.9 mcg/mL) (46). However, limitations of this study include its unblinded design, as well as a 26% withdrawal rate in the anticoagulant group (47). To further investigate the utility of anticoagulation for patients with IPF, the National Heart, Lung and Blood Institute (NHLBI) conducted the AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) trial, a double-blind randomized study comparing the administration of warfarin versus placebo in this patient population (clinicaltrials.gov identifier NCT00957242). This trial was terminated due to excess mortality in the warfarin arm (14 warfarin *vs*. 3 placebo deaths, adjusted HR=4.85), and a low probability of treatment benefit. While no significant treatment effects in quality of life measures or physiologic endpoints (FVC, 6-minute walk distance, or DlCO) were observed, higher rates of hospitalization and AE IPF were noted in the warfarin arm (48). A review by an independent Data Safety Monitoring board concluded that warfarin is unlikely to prove superior to placebo as a therapy in IPF (48). Recently, the tolerability of inhaled heparin in IPF was investigated in a small open-label pilot study under the premise that direct administration of this drug would not be associated with untoward systemic side effects of anticoagulation. No adverse effects of alveolar anticoagulation with nebulized heparin were noted in this trial (49).

Endothelin receptor antagonists and vasodilators

Animal and subsequent human studies have suggested that endothelin-1 plays a significant role in IPF (50), as it has been found to promote fibroblast proliferation (51,52), myofibroblast differentiation (52), collagen synthesis (53), and endothelial cell mitosis (54). Further, bleomycin-induced lung fibrosis in rats leads to an increase in endothelin-1 as well as increased expression of its receptor (50), and in humans, endothelin-1 has been found to be expressed at higher levels in the lung tissue of IPF patients when compared to their control counterparts (55,56).

Bosentan

The endothelin receptor antagonist, bosentan, has recently been the subject of considerable investigation. Bosentan was the subject of two large phase III blinded, randomized trials, known as the BUILD-1 and BUILD-3 studies, into which a total of 774 subjects were enrolled (clinicaltrials.gov identifier NCT00071461 and NCT00631475, respectively). Unfortunately, neither study was able to meet its primary endpoint [change in 6 minute walk test distance by month 12 for BUILD-1 (57), and death or disease progression defined by a

decline >10% in FVC and 15% in DlCO or an acute exacerbation of IPF at month 12 for BUILD-3 (58)]. While this was a well-tolerated therapy, its failure to result in significantly improved outcomes makes this a non-viable treatment option for IPF at this time (57,58).

Ambrisentan and macitentan

Other endothelin receptor antagonists, macitentan and ambrisentan, have recently been evaluated in phase II double-blind, randomized placebo controlled studies (clinicaltrials.gov identifier NCT00903331 and NCT00768300, respectively). The macitentan trial, known as the MUSIC study, enrolled 178 patients with IPF but did not meet its primary endpoint of forced vital capacity and therefore a phase III study will not be initiated. The ambrisentan trial, known as ARTEMIS-IPF, was terminated by the sponsor after an interim analysis of unblinded efficacy and safety data did not show evidence of a treatment benefit (59). Further details on these two studies have yet to be published.

Sildenafil

Sildenafil, a phosphodiesterase type-5 (PDE5) inhibitor, is today approved for use by the United States Food and Drug Administration (FDA) for idiopathic pulmonary artery hypertension (PAH) (60). Sildenafil stabilizes the second messenger of nitric oxide, cyclic guanosine monophosphate, leading to pulmonary vasodilation (61). Given that this drug seems to preferentially induce vasodilation in well-ventilated lung tissue, it is presumed that it can improve ventilation-perfusion matching (and therefore gas exchange) in IPF (61). Over one-third (33-50%) of patients with IPF undergoing formal lung transplantation evaluation have been noted to have PAH at rest as diagnosed by right heart catheterization, and the presence of PAH in those with IPF portends a poorer survival (62,63). In a small study of 14 patients with IPF (clinicaltrials.gov identifier NCT00352482), the oral administration of 25-50 mg of sildenafil three times daily for three months led to a mean improvement in 6MWD of 49.0 meters (90% confidence interval 17.5-84 meters) (64). A pilot study was thus created to further explore the potential benefit of sildenafil in IPF (clinicaltrials.gov identifier NCT00359736). Twenty-nine patients with moderately impaired pulmonary function and estimated ventricular systolic pressures (or pulmonary artery systolic pressures) of 25-50 mmHg, were randomly assigned to this double-blind, placebo-controlled study. There was unfortunately no significant improvement in 6MWD distance or dyspnea score in the sildenafil treatment group (65). Finally, 180 patients with IPF were randomized to receive oral sildenafil or placebo in a large double-blind, placebo-controlled trial called STEP-IPF (clinicaltrials.gov identifier NCT00517933) (61). The primary outcome measure (20% of the 6MWD at 12-weeks) did not meet statistical significance as only 10% in the sildenafil arm versus 7% in placebo arm showed improvement (P=0.39). There were however small but clinically significant differences in the secondary outcomes of arterial oxygenation, DLCO, degree of dyspnea and quality of life in those receiving sildenafil. Of note, data regarding the right-heart catheterization were not available in this study, thus, the presence and degree of pulmonary arterial hypertension is unknown among this study population (66). To date, there is not enough evidence to routinely support the use of sildenafil in IPF.

Antifibrotics and cytokine/kinase inhibitors

Interferon-gamma

IPF appears to be characterized by a predominantly T-helper cell type 2 cytokine state. In fact, it is very likely that the progression from inflammation to fibrosis is caused by a shift from a T-helper cell type 1 to type 2 cytokine profile state, thereby activating fibroblasts and ECM deposition and remodeling (24). Interferon-gamma (IFN-gamma) is an immunoregulatory cytokine that directly limits fibroblast proliferation and collagen synthesis. Use of IFN-gamma may actually revert the balance to one of a predominantly T-helper type 1 cytokine state (67).

IFN-gamma administration in mice has been shown to diminish bleomycin-induced lung fibrosis (28,68). In humans, a preliminary trial randomized 18 IPF patients to receive either a combination of IFN-gamma and prednisone versus prednisone only. Total lung capacity improved among those receiving IFN-gamma (from 70±6% of the predicted value at base line to 79±12% at 12 months, P<0.001 for the difference between the two groups) (69). However, a more recent study of IFN-gamma, the INSPIRE trial, did not find a significant benefit to IPF patients with respect to their primary outcome of survival (clinicaltrials.gov identifier NCT00075998). This randomized double-blinded placebo-controlled trial enrolled 826 patients with IPF to receive either IFN-gamma or placebo three times weekly (70). At their second interim analysis, the hazard ratio for mortality in patients on IFN-gamma showed no benefit compared with placebo, and the study was closed. After a median duration of 64 weeks on therapy, 15% of patients on IFN-gamma and 13% of patients on placebo had died (70). IFN-gamma is currently not recommended for the treatment of IPF.

Interest in IFN-gamma has not been lost, however, and it has been hypothesized that this compound may prove effective if delivered directly to the epithelial lining of the lung. A small pilot study involving inhaled aerosolized IFN-gamma over an 80-week period in 10 IPF patients was recently completed (clinicaltrials.gov identifier NCT00563212). Aerosolized IFN-gamma was well-tolerated and associated with a minimal change in FVC; a trend toward decreased decline in TLC and DLCO was observed post therapy (71).

Etanercept

Tumor necrosis factor (TNF)-alpha is highly expressed in the lungs of individuals with IPF, and functional polymorphisms of this cytokine are linked to an increased risk of developing IPF (28). TNF-alpha has both inflammatory and fibrogenic properties. In mouse models, for example, the injection of anti-TNF-alpha antibodies diminishes bleomycin-induced pulmonary inflammation and fibrosis (72). Furthermore, the overexpression of TNF-alpha has been found to increase fibroblasts and deposition of ECM proteins in the pulmonary interstitium (28,73). A randomized, placebo-controlled phase II trial of 65 patients with IPF was therefore conducted to assess the safety and efficacy of Etanercept, a recombinant human TNF-alpha receptor that binds to and inactivates TNF-alpha (clinicaltrials.gov identifier NCT00063869) (74). After 48 weeks of treatment, however, there was no significant improvement in the primary endpoints (change in FVC, DLCO, and $P(A\text{-}a)O_2$ at rest). Thus, the use of etanercept in patients with IPF is not advised (74).

Imatinib

The potential use of the platelet-derived growth factor receptor (PDGFR), a mitogen and chemo-attractant for mesenchymal cells such as myofibroblasts (47,75), has been studied in IPF. PDGFR mRNA is also increased in the lungs of those with IPF (76). Imatinib, an anti-proliferation protein tyrosine kinase inhibitor of PDGFR and c-kit, has prevented fibrinogenesis in bleomycin-induced fibrosis, and attenuated radiation-induced and asbestos-induced fibrosis in murine models (76). In IPF, however, a clinical phase 2 study of imatinib versus placebo (n=119) found neither a survival benefit nor effect on FVC (clinicaltrials.gov identifier NCT00131274) (77). Imatinib was also evaluated in a phase I/IIa trial in patients with systemic sclerosis-associated ILD; the drug was discontinued in 5 out of 20 patients due to adverse effects including generalized rash, diarrhea, transaminitis, myopathy, and possibly new diastolic heart failure (78).

CC-930

Activation of the stress-activated protein kinase, c-Jun N-terminal kinase (JNK), in epithelial and endothelial cells is associated with worsening fibrosis and increased inflammatory cytokine expression in IPF lungs (79). JNK induces tissue factor expression (80), which in turn drives thrombin production and fibrin generation (81). Inhibition of JNK in human lungs fibroblasts prevents differentiation to the myofibroblast phenotype by Transforming Growth Factor-beta1 (TGF-β1) (82). Bleomycin induces epithelial cell death through a JNK-dependent mitochondrial death pathway in rodents (83), and mice lacking JNK are protected against TGF-β1 and bleomycin-induced lung fibrosis (84). Inhibition of JNK could therefore potentially serve a therapeutic end in IPF. The safety of CC-930, an antifibrotic inhibitor of JNK (85), was recently tested in a phase II clinical trial (clinicaltrials.gov identifier NCT01203943). The trial, however, was terminated by the sponsor, citing that the benefit/risk profile did not support its continuation as rationale for its early end (86).

Treatments under investigation

Antioxidant/immunosuppressant/antiiflammatory therapies

N-acetylcysteine

N-acetylceysteine (NAC) is a precursor to the antioxidant glutathione. Glutathione has been found to be depleted in the lungs of those with IPF (4). NAC has been viewed as a potentially effective therapeutic regimen in IPF in the hope that repletion of glutathione stores would restore natural oxidant/anti-oxidant balance to prevent the oxidative injury that precedes fibroproliferation (4). In a non-randomized prospective study of 18 patients, the addition of NAC to the current therapy (corticosteroid ± immunomodulator) revealed improved lung function measures (87). The use of NAC was thus explored prospectively with 155 patients randomized to receive treatment (NAC) or placebo in addition to prednisone and azathioprine in the IFIGENIA trial (clinicaltrials.gov identifier NCT00639496) (88). At 12 months, the use of NAC slowed down the decline in vital capacity (relative difference of 9%, P=0.02) and DLCO (relative difference of 24%, P=0003). There was however no survival benefit in the treatment arm. Of note, this study had a large drop-out rate and, by 12 months, 30% of patients had died or were lost to follow-up.

The NHLBI designed the ongoing PANTHER-IPF trial to evaluate the effectiveness of the combination of prednisone, azathioprine, and N-acetylceysteine (NAC) *vs*. NAC alone *vs*. placebo (clinicaltrials.gov identifier NCT00650091) (66). After 155 of the 390 planned patients were enrolled, a data safety monitoring committee recommended that the combination treatment arm of this trial be stopped. This was based upon the discovery that, when compared to placebo, the three-drug regimen led to a significant increase in mortality (11% *vs*. 1%), hospitalizations (29% *vs*. 8%) and serious adverse events (31% *vs*. 9%), and did not show an improvement in pulmonary function (89). While recent IPF treatment guidelines listed this three-drug combination therapy as a weak recommendation (1), it had until very recently been commonly viewed as the default standard of care for IPF. Subjects in the PANTHER-IPF trial arms receiving NAC alone and placebo continue to be followed. To date, there exist too few data to recommend NAC monotherapy in IPF (1).

Antifibrotic/antiinflammatory/antioxidants

Pirfenidone

Pirfenidone, an orally administered pyridine, is the only drug

approved for clinical use in the treatment of IPF worldwide (90). It is an anti-inflammatory and antioxidant agent that inhibits transforming growth factor-β *in vitro* (91). Pirfenidone also acts as an antifibrotic by directly altering the expression, synthesis, and possibly accumulation of collagen, and inhibiting the recruitment, proliferation and possibly expression of the extracellular matrix-producing cells (90). Based on favorable results in two open-labeled compassionate use studies followed by a Japanese phase II trial, three randomized, double-blind, placebo-controlled, multicenter, phase III studies were conducted. Two of these were the almost identical multinational 004 and 006 trials (referred to as the CAPACITY studies), and the third trial was conducted in Japan (92,93).

In the 004 trial, 435 patients with IPF were assigned in a 2:1:2 dosing ratio to 2,403 mg/day pirfenidone, 1,197 mg/day prifenidone, and placebo (92). In the 006 study, 344 patients were assigned to either 2,403 mg/day of pirfenidone or to placebo. In study 004, pirfenidone reduced the decline in FVC (P=0.001), with a mean reduction at 72 weeks of 8% (SD 16.5) in the 2,403 mg/day group and a reduction of 12.4% (SD 18.5) at 72 weeks in the placebo group (difference 4.4%, 95% CI, 0.7 to 9.1). However, in study 006, the change in FVC at 72 weeks was not significant between the treatment and placebo arms (P=0.501) (92). It was largely based on these studies that pirfenidone was approved by the European Commission (EC) in 2011 (94) for the treatment of mild to moderate idiopathic pulmonary fibrosis.

In the double-blind, placebo-controlled randomized Japanese trial by Taniguchi *et al.*, pirfenidone was administered in a 2:1:2 ratio (1,800 mg/day, 1,200 mg/day or placebo) to a total of 275 patients over a 52 week period (93). The primary endpoint, a change in lung vital capacity, was significantly preserved in the higher dose versus placebo group (–0.09 *vs.* –0.16 L respectively, P=0.0416). Limitations to this study include the enrollment of a relatively homogeneous Japanese population, as well as the fact that the primary end-point was changed before unblinding. Furthermore, the change in primary endpoint was recommended by the members of the data safety and monitoring board after review of interim comparative data of the primary and secondary end points, possibly compromising the integrity and credibility of the trial (95). The study also observed a significant progression-free survival time (a secondary end-point) between these two groups (P=0.0280). In an exploratory analysis of this study later published by Azuma *et al.*, it was observed that a subpopulation of these patients (those with a baseline predicted VC ≥70% and oxygen saturation <90%) had a greater benefit from pirfenidone (96). A well-known side effect of pirfenidone, photosensitivity, was frequently observed in this study (51% of patients in the high-dose group and 53% in the low-dose group). Pirfenidone was approved in 2008 for use in the management of IPF in Japan by the Japanese Ministry of Health, Labour and Welfare, in part because of this study (97). Despite its approval by both the EU and Japan, due to concerns including a perceived lack of efficacy as measured by change in FVC, and lack of survival benefit, the use of pirfenidone for IPF has not been approved by the FDA (98). A new phase III trial of pirfenidone aiming to detect a clinically meaningful effect on forced vital capacity is therefore underway in the United States (the ASCEND trial, clinicaltrials.gov identifier NCT01366209).

Targeting cytokine networks involved in immune and structural cell activation

Inhibition of transforming growth factor-β (TGF-β)

In animal models, TGF-β, a pleitropic cytokine, is increased prior to collagen synthesis, and in lungs of individuals with pulmonary fibrosis, immunohistochemical staining reveals increased TGF-β, most notably in areas of regeneration and remodeling (99). TGF β exists in 3 isoforms in mammals (100), and a growing body of evidence suggests that one of these, TGF-β1, is a key pro-fibrotic agent. Its activity is characterized by the promotion of extracellular matrix production (101), fibroblast to myofibroblast differentiation (100), and inhibition of autophagy in fibroblasts (102). These insights have made TGF-β1 an important ongoing therapeutic target in IPF. A Phase I trial of GC1008, an antibody targeting all TGF-β isoforms, has recently been completed (clinicaltrials.gov identifier NCT00125385), however, the results of this study are not yet available.

TGF-β plays a key role in cellular homeostasis, acting as a tumor suppressor under certain circumstances (103). Because patients with IPF are at increased risk for developing lung cancer (104), the direct inhibition of TGF-β could potentially result in very undesirable side effects (28). The TGF-β activation cascade therefore poses a more attractive therapeutic target. Partial inhibition of αvβ6 integrin, a key activator or TGF-β1, has been shown to prevent bleomycin-induced pulmonary fibrosis without exacerbating inflammation in mice (105). A humanized monoclonal antibody against αvβ6 integrin, STX-100 is currently under evaluation in a randomized, placebo-controlled phase II IPF trial (clinicaltrials.gov identifier NCT01371305).

Other members of the TGF-β superfamily, bone morphogenic proteins (BMPs), are also involved in injury repair and homeostasis. Interestingly, a BMP antagonist, gremlin, is upregulated in IPF lung biopsies. In mice exposed to asbestos, those treated with BMP had reduced fibrosis. In fact, markers of collagen deposition in the lung were decreased by 50%, suggesting that the preservation of BMP activity may be of therapeutic value in IPF (106).

Inhibition of connective tissue growth factor (CTGF)

Connective tissue growth factor (CTGF), a matricellular protein,

is thought to be a central mediator of tissue remodeling and fibrosis. It is highly expressed in IPF fibroblasts (107) and in bleomycin-challenged mice (108). CTGF is induced by TGF-β, and mediates some of the profibrotic effects of TGF-β (100); it also activates type-1 collagen expression (108). Anti-CTGF antibodies have been shown to decrease collagen-1 gene activity. In murine models of multiorgan fibrosis caused by the administration of CTGF and TGF-β and in bleomycin-induced lung fibrosis, the administration of a human CTGF antibody, FG-3019, results in reduced histological signs of fibrosis (109). Preliminary safety and efficacy data from an open-label, phase II trial of FG-3019 (clinicaltrials.gov identifier NCT01262001), were recently presented at the European Respiratory Society 2012 conference (110). While this trial is still ongoing and not all data have been analyzed, improvement or stability of fibrosis as determined by HRCT scan quantification was apparent in 14 of 25 IPF patients after 24 weeks of treatment with FG-3019, and this improvement was positively associated with changes in FVC (110). While these preliminary findings are promising and a randomized, placebo-controlled trial of FG-3019 is planned, it is important to note that the results of this study have not yet been published in a peer-reviewed publication.

Somatostatin analogues

Expression of receptors for somatostatin, a regulator of growth hormone secretion also known as a growth hormone-inhibiting hormone, is increased in human IPF lungs (111). The somatostatin analog SOM230 has been observed to have an antifibrotic effect in bleomycin-induced lung fibrosis in mice, resulting in a decreased expression of TGF-β and CTGF (112). Treatment with octreotide, another somatostatin analogue, has shown to decrease parenchymal fibrosis and structural deformities in the bleomycin model (113). Somatostatin analogues therefore merit evaluation as therapeutic agents for IPF. Octreotide was recently tested in a small non-randomized open-label study. Twenty-five IPF patients were enrolled to receive octreotide, and 17 completed the study, receiving treatment over a 48-week period (clinicaltrials.gov identifier NCT00463983). Compared to historical controls (subjects from other published IPF trials), the rate of decline in pulmonary function (FVC and DlCO) was lower in subjects treated with octreotide (114). Octreotide thus remains a potentially useful agent for the treatment of IPF; however, larger randomized, controlled trials are necessary to confirm this.

Inhibitors of IL-13, IL-4 and CCL2

Another driver of lung fibrosis is the cytokine expressed by T helper type 2 lymphocytes, interleukin-13 (IL-13), which, through the chemokine CCL2, upregulates TGF-β1 to stimulate fibrosis, as observed in a murine model. In humans, IPF fibroblasts are hyper-responsive to TGF-β1, IL-13, and to CCL2, and it has been suggested that these molecules may each mediate the function of the other in a pro-fibrotic manner. Inhibition of CCL2 orthologs resulted in reduced collagen deposition in an in-vivo bleomycin model. CCL2 is a known fibrocyte chemoattractant (107), further, high CCL2 levels may be correlated with progression of IPF (115). IL-13 has also been observed to stimulate collagen deposition and myofibroblast differentiation both independently and with the help of TGF-β1 (116). CCL2 and IL-13 therefore pose attractive therapeutic targets in IPF. Phase II trials of CNTO888 and QAX576, CCL2 and IL-13 antibodies, respectively, have recently been completed. The results of both trials are awaited (clinicaltrials.gov identifier NCT00786201 and NCT00532233). Tralokinumab, a human recombinant monoclonal antibody for IL-13 is currently being tested for IPF in a phase II randomized, placebo-controlled trial (clinicaltrials.gov identifier NCT01629667).

Interleukin 4, a cytokine structurally related to IL-13, has also been implicated in the abnormal proliferation of fibroblasts that characterizes IPF (117). Both IL-13 and IL-4 are elevated in the bronchial alveolar lavage fluid of IPF patients (118) and increased expression of the receptors that bind IL-4 and IL-13 has been detected in fibroblasts grown from surgical lung biopsies of patients with UIP as compared to those from patients with other idiopathic interstitial pneumonias and patients without lung fibrosis. Further, the proliferation of UIP-derived fibroblasts is inhibited when exposed to the cytotoxic effects of a Pseudomonas exotoxin targeting the IL-13 and IL-4 receptors, suggesting that fibroproliferation in UIP can be modulated by agents targeting these cytokines (119). To this end, a randomized, double-blind, placebo-controlled study of an engineered bispecific antibody targeting both IL-4 and IL-13, SAR156597 (120), is now enrolling patients with IPF (clinicaltrials.gov identifier NCT01529853).

Thalidomide

Although thalidomide is to blame for some of the most infamously tragic adverse effects in modern medicine, it has recently been used effectively for treating multiple myeloma and other conditions. Thalidomide is an anti-angiogenic (121), immunomodulatory (122), anti-inflammatory (123) drug. Thalidomide administration can attenuate fibrosis in bleomycin-challenged mice, possibly through the inhibition of TGF-β1-induced signaling pathways (124) and a reduction of vascular endothelium growth factor (VEGF) expression (125). An open-label study to determine the safety, feasibility and efficacy of this potential anti-fibrotic agent concluded in 2007, however, the results have not been published (clinicaltrials.gov identifier NCT00162760). Thalidomide also represents a promising therapeutic agent for a debilitating symptom affecting nearly 80% of IPF patients that is refractory to current treatments: severe, persistent cough. Recently, a phase III randomized, double-blind study of 98 IPF patients with chronic cough demonstrated that

thalidomide can improve cough and symptom-specific quality of life (126) (clinicaltrials.gov identifier NCT00600028).

Inhibition of LOXL2

The enzyme lysyl oxidase-like 2 (LOXL2) generates the scaffold on which fibroblasts grow by cross-linking fibrillar collagen. This enzyme is apparently over-expressed in IPF lungs and associated with activated fibroblasts, reactive pneumocytes, and vasculature in fibrotic foci (127). Inhibition of LOXL2 results in reduced levels of activated fibroblasts and TGF-β pathway signaling in human fibroblasts and bleomycin-treated mice (127). An allosteric inhibitor of LOXL2, the humanized monoclonal antibody GS-6624 (formerly AB0024), was evaluated in a phase I trial for the treatment of IPF (clinicaltrials.gov identifier NCT01362231), and a phase II trial is planned.

Targeting angiogenesis and ECM collagen deposition

While angiogenesis may exist as a mechanism to promote alveolar repair in fibrosing lung disease, its role may well be pathogenic in IPF. New blood vessel formation is regulated by angiogenic and angiostatic factors that respectively promote or inhibit neovascularization (128). Angiogenic chemokine expression is reportedly increased in IPF (129), and low levels of angiostatic chemokines have been observed in bleomycin-induced fibrosis (130). Paradoxically, the angiostatic chemokine, pigment epithelium-derived factor (PEDF), has also been noted to be elevated in IPF lungs. PEDF however is regionally associated with heterogeneous vascularization, characterized by a near absence of vessels within the fibroblastic foci, more prominent vascularity in the areas of fibrosis around the fibroblastic foci, and abnormal vessels in the most architecturally distorted regions (131). This heterogeneity may support fibroproliferation whilst inhibiting normal repair mechanisms (132).

Tyrosine kinase inhibitor BIBF 1120

BIBF 1120 is a tyrosine kinase inhibitor that suppresses pro-angiogenic intracellular signaling by targeting the proliferative growth factor receptors in fibroblasts (FGFR), platelets (PDGFR), and the vascular endothelium (VEGFR) (133). Blockade of these receptors may be therapeutic in IPF as their activation has been implicated in the pathogenesis of fibrosis (134-136). A phase IIb 12-month, randomized, double-blind, placebo-controlled study of BIBF 1120 was recently conducted to evaluate its safety and efficacy in IPF. This study, called the TOMORROW trial, demonstrated a trend toward a reduction in the decline in lung function, with fewer acute exacerbations and preserved quality of life in IPF patients (137). This prompted two currently ongoing, nearly identical phase-III randomized, placebo-controlled studies to further investigate the efficacy of BIBF 1120 in IPF (the INPULSISTM trials; clinicaltrials.gov identifiers NCT01335464 and NCT01335477).

Tetrahiomolybdate and minocycline

Administration of angiostatic chemokines and other agents with angiostatic properties such as tetrahiomolybdate, has been observed to reduce both angiogenesis and fibrosis in the bleomycin model (138-140). Minocycline hydrochloride, a broad-spectrum tetracycline antibiotic with anti-inflammatory and anti-angiogenic properties (141), was evaluated in a phase III clinical study of IPF patients (clinicaltrials.gov identifier NCT00203697). The safety of tetrahiomolybdate, was also evaluated in IPF in a phase I trial (clinicaltrials.gov identifier NCT00189176). Although both studies have concluded, their results are yet unknown (142).

Doxycycline

A key feature of IPF is the excessive deposition of extracellular matrix and basement membrane disruption that may be at least in part due to an imbalance between secreted matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) that results in a relative overexpression of TIMPs (143). In spite of their ability to break down the ECM, several MMPs (1 through 3 and 7 through 9) are paradoxically highly upregulated in IPF lungs (27,143-145). One possible explanation for the association between high MMP levels and fibrosis is that MMPs may be mainly expressed outside of the interstitial compartment where collagen is accumulating (146). However, these proteinases may in fact promote a fibrotic response as a result of their multiple biological functions outside of collagenolysis including apoptosis, migration, proliferation and angiogenesis (147). Matrylisin (MMP-7), for example, regulates TGF-β activity via the release of pre-formed TGF-β from the extracellular matrix (147), and interacts with osteopontin, an inflammatory cytokine that promotes extracellular matrix deposition and induces growth and migration of fibroblasts and epithelial cells (148). Inhibition of MMPs therefore represents an attractive therapeutic target in IPF. Doxycyline, an MMP inhibitor (149), has been observed to attenuate fibrosis, inhibiting MMPs, collagen-1, TGF-β, and CTGF in human type II AECs and bleomycin-exposed mice (150). Doxycycline was tested in two open-label studies performed in India, and a non-statistically significant trend toward improved 6mwt and FVC was observed (151,152). These studies were quite small (n=6 patients each), however, and doxycycline may merit further investigation in larger, controlled clinical trials.

Targeting the renin-angiotensin system

The renin-angiotensin system is a key regulator of blood pressure homeostasis. Renin, a protease, cleaves its only known substrate (angiotensinogen) to form angiotensin I, which in turn serves as substrate to angiotensin converting enzyme (ACE) to form ANGII. Renin and ANGII have both been implicated in IPF pathogenesis.

ANGII is a powerfully vasoactive hormone whose pleitropic effects are mediated by two receptors highly expressed in IPF lungs: angiotensin type 1 (AT1) and angiotensin type 2 (AT2) (153). ANGII induces apoptosis in alveolar epithelial cells (154) and pulmonary arterial endothelial cells (155), and the proliferation, activation, and migration of fibroblasts, resulting in abnormal deposition of ECM components (153). Myofibroblasts from IPF lungs synthesize more ANGII and active TGF-β than fibroblasts from normal lungs, with ANGII driving the production of this pro-fibrotic cytokine and resulting in increased myofibroblast differentiation in a process that has been described as an "angiotensin/TGF-β1 autocrine loop. (156)" Bleomycin-induced lung injury is attenuated by administration of ACE inhibitors (ramipril or captopril) (157), or an AT1 inhibitor (losartan) (158,159), or deletion of the AT1 gene (158). Inhibition of ANGII or its receptors thus represents an attractive target for the treatment of IPF, and the safety and efficacy of losartan are currently being investigated in a phase II open-label clinical trial of IPF (clinicaltrials.gov identifier NCT00879879).

It is unclear whether the use of ACE inhibitors is efficacious in human lung fibrosis, however, as a lack of observed benefit has been reported in some studies (160,161). ACE2, another regulator of the renin-angiotensin system that converts ANGII into its anti-apoptotic degradation product ANG1-7, is notably underexpressed in IPF lungs (162). ANG1-7 inhibits the activation of JNK, in effect regulating AEC survival (163), and the systemic administration of purified recombinant ACE2 has been shown to reduce bleomycin-induced lung collagen deposition in mice (162). It has therefore been suggested that the excessive signaling by ANGII may be due to its impaired degradation and the loss of an inhibitory signal rather than to its increased synthesis, and that agents that enhance ANGII metabolism, such as ACE2, may thus be effective against lung fibrosis (164).

Renin has recently also been noted to be a pro-fibrotic mediator of lung fibrosis that functions independently from ANGII. Its effects in human IPF lungs and fibroblasts include a marked increase in TGF-β and collagen. Renin gene silencing results in the reduced expression of collagen and TGF-β1 in vitro. Renin inhibition could thus potentially ameliorate IPF fibrosis (165).

Other potential therapies for IPF

Carbon monoxide

The enzymatic product of heme oxygenase activity, carbon monoxide (CO), is a biologically active diatomic gas endogenous to healthy and diseased humans. CO has well-described anti-proliferative properties (166-168), and there is evidence that CO is protective in the setting of lung injury (169,170). Short, transient exposure to CO has also demonstrated to reduce fibrosis in the bleomycin model (171). It is thought that the antifibrotic effects of CO may be at least in part due to its inhibition of TGF-β-induced ECM constituents fibronectin and type I collagen production in fibroblasts (171). Futher, administration of quercitin, an inducer of heme oxygenase, results in the attenuation of TGF-β-stimulated collagen production in human fibroblasts (172). While the mechanisms driving the antifibrotic properties of CO have not yet been fully elucidated, low-dose inhaled CO is currently being tested as a potential IPF therapy in a phase II trial (clinicaltrials.gov identifier NCT01214187).

Adjunctive treatment of gastroesophageal reflux

The prevalence of gastroesophageal reflux (GER), symptomatic or "silent," has been estimated to be as high as 88% in IPF patients (173,174), prompting the hypothesis that injury to the lung tissue caused by repeated microaspiration triggers the development of fibrosis (175). While it is possible that GER may develop as a consequence of anatomical remodeling caused by progressive fibrosis, data from animal studies (176,177) and small human case series (178,179) support the role of GER as pathogenic for IPF. One recent observational study of 204 IPF patients from two centers revealed an association between GER medication use [in the form of proton pump inhibitors (PPIs) or histamine-2 receptor (H2) blockers] and improved survival (HR=0.47), along with a decreased HRCT fibrosis score (14% compared to 19% in those not taking medications) (180). While these results suggest that GER therapy may be of benefit in IPF, further study is needed to demonstrate a causal relationship to improved survival.

Stem cell therapy

Restoration of the alveolar epithelium is of course the most desirable of therapeutic effects in the setting of IPF. When the lung is injured, there is an intense production of inflammatory signaling molecules to recruit progenitor cells and stem cells to the site of injury to restore the integrity of the epithelial layer and alveolar capillary units (181). In IPF, however, a premature exhaustion of the renewal potential of epithelial stem cells, possibly caused by telomere shortening in the setting of environmental insult (e.g., smoking, pollution), is one probable cause of the loss of epithelial integrity and abnormal alveolar re-epithelialization (182). Promisingly, pluripotent stem cells derived from embryonic or adult tissues can differentiate into lung epithelial and endothelial cells, ameliorating lung injury and fibrosis as demonstrated in several preclinical studies (181,183-188). Although it is not clear whether structural engraftment or a paracrine/immunomodulatory effect produced by the stem cells is responsible for these potentially therapeutic effects (189), this therapy could potentially result in the regeneration and repair of diseased adult lungs. One recent study of intravenous mesenchymal stem cell therapy to restore the myocardium after acute infarction revealed that a majority of these

cells were sequestered by the lung, and this was associated with improvement in the pulmonary function of treated subjects (190). It is important to note, however, that pluripotent cells have been associated with spontaneous transformation and induction of malignancy, and it is also possible that their great plasticity could lead to differentiation into unwanted cell phenotypes with untoward effects (189,191). Nevertheless, a Phase I, open-label safety and feasibility study of mesenchymal stem cell treatment for IPF in up to 8 subjects was started in Australia (clinicaltrials.gov identifier NCT01385644). While the enrollment status or results of this trial are not yet published, the US FDA very recently approved the first clinical trial of intravenous mesenchymal stem cell therapy for IPF, a phase I study yet to be listed in clinicaltrials.gov.

Lung transplantation

At present, the only intervention that improves survival in select patients with IPF is lung transplantation. In a study of 46 patients awaiting lung transplantation, survival was increased by 79% one year post transplant, and the relative risk reduction for those who underwent lung transplantation was 75% (P=0.03) compared to patients who remained on the waiting list (192). Despite its success, lung transplantation is not without significant risks. The most common complications and causes for poor long-term survival after transplantation include infection (given the need for immunosuppression), acute and chronic graft rejection, and airway stenosis (193). The general age cut-off for lung transplantation is 65 years, while there are exceptions based on the patient's functional capacity and comorbidities (193). Of note, the adoption of the newer lung allocation score system has resulted in significant reduction in both wait times and mortality on the wait list for IPF patients (66). More recently, bilateral lung transplantation (BLT) has become preferred when compared to single lung transplantation (SLT). Data from the International Society for Heart and Lung Transplantation demonstrated that between January 2000 to June 2005, 1- and 5- year survival rates for SLT in IPF were 76% and 45% respectively (n=1,084), and for BLT were 77% and 52.5% respectively (n=687) (194).

The general guidelines for lung transplantation include a baseline carbon monoxide diffusing capacity (DLco) of less than 35% to 39% predicted, a desaturation during a 6MWT to less than 88%, and a decline in the FVC of 10% or greater when compared over a 6-12 month period of time (193). Nevertheless, guidelines for referral and listing for transplantation by the International Society for Heart and Lung Transplantation recommend referring patients with IPF (with histologic or radiographic evidence) for transplant evaluation early, regardless of the FVC parameters (193,195). In fact, data from a recent single-center prospective study reveal that a delay from onset of dyspnea until evaluation at a tertiary care center is associated with a higher rate of death from IPF independent of disease severity (196).

Clinical trials

Recently completed and ongoing studies are summarized in Tables 2 and 3, respectively. Over the past decade, the definition of IPF and thus enrollment criteria for this disease have become more specific, however, study design still remains a challenge as there is continued debate on what constitutes a clinically meaningful endpoint. While all-cause mortality and all-cause non-elective hospitalization have been proposed as the best choices (197), measuring these outcomes could be prohibitive, requiring the enrollment of a large number of patients to be followed over an extensive period of time. Others have proposed that the widely adopted primary endpoint of lung function, specifically FVC, is in fact clinically meaningful. Nevertheless, due to the dearth of therapeutic agents approved for the treatment of IPF, patients should be strongly encouraged to participate in randomized, multi-center, placebo-controlled trials (1,193). A registry of federally that privately supported clinical trials at "clinicaltrials.gov" lists active or recently completed studies of IPF and can be accessed by referring physicians (193).

Conclusions

Over the past 10 years, substantial advances have been made in the understanding of the pathophysiology of IPF. As new pathogenic pathways and mediators are discovered, new therapies in development are more sharply focused on the fibroblastic process, sharing as their target abnormal tissue remodeling, excessive extracellular matrix accumulation, and angiogenesis, all believed to be at the heart of this progressive disease. While it is likely that any effective treatment strategy for IPF will need to target more than one of the pro-fibrotic pathways associated with its complex pathogenesis, only one therapeutic agent has been approved to date worldwide. The development of new treatment modalities is therefore critically important. Although the mechanisms underlying this disease remain poorly understood, the advances that have been made to date provide us with hope for the discovery and development of effective treatment modalities in the near future.

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Table 2. An overview of select clinical trials of in IPF - Unsuccessful Treatments to Date. (Modified from Datta *et al.*, 2011)

Agent/treatment	Potential mechanism of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/available	Outcome/comments
Corticosteroids	Suppression of cellular and humoral immunity; reduction of proinflammtory molecules	Significant lack of studies evaluating prednisolone against placebo Flaherty *et al*. (2001)	None available	Open label study; (*n*=41)	Primary end point: CRP score at 3 months	27% responders/ 46% stable/ 27% non-responders. Adverse effects noted in all patients Cochrane Review of 2003 found no evidence for an effect of corticosteroids in IPF; no high quality prospective studies were identified as suitable for meta-analysis (Richeldi *et al*., 2003)
Azathioprine as adjunctive to prednisolone	Inhibits adenine deaminase and impairs cell proliferation (particularly leukocytes); anti-inflammatory	Raghu *et al*. (1991)	None available	Prospective, double-blinded, randomized placebo-controlled trial; prednisolone + azathioprine (*n*=14) *vs*. prednisolone + placebo (*n*=13)	Primary end points: ΔFVC/DL_{co}/A-a gradient at 1 year; survival at 9 years	Marginally significant survival benefit in azathioprine + prednisolone group only after age-adjustment No significant improvement in remaining parameters
Azathioprine + prednisolone	As above	Thorax National Institute, Chile	NCT00518310	Prospective, double-blinded, randomized trial; Azathioprine + prednisolone *vs*. placebo; planned enrollment (*n*=100)	Primary end point: progression free survival at 2 years	Trial status unknown; results awaited
Cyclophosphamide	Alkylating agent with anti-inflammatory properties	Collard *et al*. (2004)	None available	Retrospective case series; cyclophosphamide + prednisolone *vs*. no treatment; (*n*=82) in each group	Primary end point: Survival at 6–12 months	No evidence for a therapeutic benefit. Significant potential adverse effects
Everolimus	Immunosuppressant-macrocyclic proliferation cyclic inhibitor	Malouf (2011)	ANZCTR 12605000599673	Prospective, double-blinded, randomized placebo-controlled trial; everolimus (*n*=44) *vs*. placebo (*n*=45)	Primary end point: Δ6MWD, arterial oxygen saturation, quality of life, and dysnpea score up to 36 months	Trial completed; increased time to disease progression in treatment group. 180 days *vs*. 450 days for placebo group. 48% of patients in treatment arm did not tolerate an 8mg dose. 23% of these patients discontinued for this reason

Table 2 (*continued*)

Table 2 (continued)

Agent/treatment	Potential mechanism of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/available	Outcome/comments
Warfarin	Anticoagulation via inhibition of Vitamin K reduction	Kubo *et al*. (2005)	None available	Randomized open label trial; prednisolone + warfarin/low molecular weight heparin(n=31) *vs*. prednisolone + placebo (n=33)	Primary end points: time to death and hospitalization-free time over 1 year	Anti-coagulant therapy resulted in a significant increase in survival of patients with IPF and a significant improvement in survival associated with acute exacerbations of IPF
Warfarin	As above	ACE-IPF trial NHLBI – Duke University, USA Noth *et al*. (2012)	NCT00957242	Prospective, double-blinded, randomized placebo-controlled trial; warfarin *vs*. placebo; currently recruiting, planned enrollment (n=256)	Primary end points: time to death or disease progression over 48 weeks	Trial terminated; excess mortality in warfarin arm (14 warfarin *vs*. 3 placebo deaths). Low probablity of treatment benefit. Higher rates of hospitalization and acute exacerbation.
Heparin	Anticoagulation via inhibition of thrombin and other proteases.	Markart *et al*. (2010)	None available	Open label exploratory study evaluating safety of nebulized heparin in IPF; (n=21)	Study designed to assess safety and tolerability	Trial completed; adequate local anticoagulation achieved with no significant adverse effects. Future trials planned to evaluate efficacy.
Bosentan	Endothelin-1 (ET) receptor antagonist; ET promotes fibroblast proliferation, differentation, collagen synthesis, and endothelial cell mitosis	BUILD-1 trial King *et al*. (2008)	NCT00071461	Prospective, double-blinded, randomized placebo-controlled trial; bosentan (n=74) *vs*. placebo (n=84)	Primary end point: 6MWD at 12 months	Trial completed; no effect on primary outcome between treatments arms; *post hoc*analysis demonstrated trend in delayed time to disease progression or death in the bosentan arm of IPF patients who had undergone lung biopsy
Bosentan	As above	BUILD-3 trial (Actelion, Switzerland)	NCT00631475	Prospective, double-blinded, randomized placebo-controlled trial; total (n=616), bosentan : placebo 2:1 recruitment complete	Primary end points: time to disease progression or death over 8-32 months	Trial terminated at interim analysis stage due to lack of efficacy

Table 2 (*continued*)

Table 2 (continued)

Agent/ treatment	Potential mechanism of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/ available	Outcome/comments
Ambrisentan	As above	ARTEMIS-IPF trial (Gilead, USA)	NCT00768300	Prospective, double-blinded randomized placebo-controlled trial; ambrisentan *vs.* placebo, currently recruiting, planned enrollment (n=600)	Primary end points: time to disease progression or death, event driven over 4 years	Trial terminated at interim analysis stage due to lack of efficacy
Macitentan	As above	MUSIC trial (Actelion, Switzerland)	NCT00903331	Prospective, double-blinded randomized placebo-controlled trial; total n=178; macicentan *vs.* placebo, recruitment complete	Primary end point: ΔFVC over 12 months	Trial terminated; did not meet primary endpoint between treatment arms of FVC
Sildenafil	Phosphodiesterase 5 inhibitor. Causes vasorelaxation by stabilizing cGMP	Step-IPF Clinical Research Network, USA (Zisman *et al*., 2010)	NCT00359736	Prospective, double-blinded, randomized placebo-controlled trial :sildenafil (n=89) *vs.* placebo (n=91). Double-blind study over initial 12 weeks, followed by open label extension for 12 weeks with all patients receiving sildenafil	Primary end points: Δ 6MWD over 12 weeks Secondary end point: dyspnea score at 6 months	Trial completed; No significant improvement in primary end point in treatment arm, but significant improvement in secondary end points in sildenafil arm, including DL_{co} and quality of life score
Interferon (IFNγ1b)	Immunoregulatory cytokine limiting fibroblast proliferation and collagen synthesis	INSPIRE trial King *et al*. (2009)	NCT00075998	Prospective, double-blinded, randomized placebo-controlled trial; interferon (n=551) *vs.* placebo (n=275)	Primary end point: survival from time of randomization	Trial ended prematurely; overall survival had crossed predefined boundary at planned interim stage analysis (64 weeks); however, no difference between treatment and placebo arms

Table 2 (*continued*)

Table 2 (continued)

Agent/treatment	Potential mechanism of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/available	Outcome/comments
Inhaled IFNγ1b	As above	National Centre for Research Resources, USA Diaz *et al*. (2012)	NCT00563212	Non-randomized, open-label, single interventional study with nebulized interferon-γ Recruiting patients; planned enrollment *n*=10	Primary end point: safety and tolerability Secondary end points: lung function trends and BALF [IFN-γ] at 1 year	Trial completed; aerosolized IFNγ1b was well tolerated and associated with minimal change in FVC over 80 weeks and a decreased slope of decline in TLC and DICO
Etanercept	TNFα inhibitor -anti-inflammatory, anti-fibrogenic	Raghu *et al*. (2008)	NCT00063869	Prospective, double-blinded, randomized placebo-controlled trial; etanercept (*n*=34) *vs*. placebo (*n*=31)	Primary end points: Δ FVC, DL_{co}/ΔA-a gradient over 48 weeks	Trial completed; no significant difference observed between treatment groups. Etanercept therapy resulted in a non-significant reduction in disease progression in several physiological, functional and QoL end points
Imatinib mesylate	Inhibitor of PDFG and TGFβ signaling, which promote fibroblast to myofibroblast transformation and proliferation and ECM production	Daniels *et al*. (2010)	NCT00131274	Prospective, double-blinded, randomized placebo-controlled trial; imatinib (*n*=59) *vs*. placebo (*n*=60)	Primary end point: time to disease progression (>10% decline in predicted FVC) or death over 92 weeks	Trial completed; no change in primary end point between treatment and placebo
CC-930	JNK inhibitor-JNK induces tissue factor expression and thrombin and fibren generation	Celgene Corporation	NCT01203943	Prospective, double-blinded, randomized placebo-controlled trial; planned enrollment *n*=28	Primary end point: safety up to 4 weeks of treatment Secondary end point: pharmacokinetics and long-term safety	Trial terminated at interim analysis stage due to unfavorable risk benefit profile.

6MWD, 6 min walk test distance; A-a, alveolar:arterial ANZCTR, Australian New Zeland clinical trials registry; BALF, bronchoalveolar lavage fluid; CCL-2, Chemokine (C-C motif) ligand 2; cGMP, cyclic guanosine monophosphate; CRP, clinical-radiographic-physiological; DLco, carbon monoxide dilution; FGFR, fibroblast growth factor receptor; FVC, forced vital capacity; H2, histamine H2 receptor blocker; HRCT, high resolution computer tomography; IFN-γ, interferon-gamma; IL-13, interleukin 13; IL-4, interleukin 4; LOXL-2, lysyl oxidase-like enzyme 2; MMP, matrix metalloproteinase; NCT, clinicaltrials.gov identifier; PDGFR, platelet-derived growth factor receptor; PPI, proton pump inhibitor; pred, predicted QoL, quality of life; TGFβ, transforming growth factor-beta; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Permission has been obtained from John Wiley and Sons for reuse of figure Table 2.

Table 3. An overview of select clinical trials of in IPF - Treatments Under Investigation (Modified from Scotton and Chambers, 2007 and Datta and Scotton, 2011 BJP).

Agent/treatment	Potential mechanisms of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/available	Outcome/comments
Azathioprine + Prednisolone with or without N-acetylcysteine (NAC)	Antioxidant, immunosuppressant, anti-inflammatory	IFIGENIA trial Demedts *et al*. (2005)	NCT00639496	Prospective, double-blinded, randomized placebo-controlled trial; NAC + azathioprine + prednisolone ($n=92$) *vs*. placebo + azathioprine + prednisolone ($n=90$)	Primary end points: absolute ΔFVC and DL_{co} at 12 months	Trial completed; reduction in FVC and DL_{co} decline over 1 year in NAC arm, though no change in mortality
N-acetylcysteine (NAC) with or without Azathioprine + Prednisolone	Antioxidant, immunosuppressant, anti-inflammatory	Panther-IPF trial NHLBI, USA Raghu *et al*. (2012)	NCT00650091	Prospective, double-blinded, randomized placebo-controlled trial; currently recruiting patients, planned enrollment $n=390$	Primary end point: ΔFVC at 60 weeks	Increased mortality observed in the triple therapy arm. Triple treatment arm stopped for safety. Subjects on NAC or placebo alone continue to be followed
Pirfenidone	Antifibrotic inhibitor of TGFβ, anti-inflammatory, antioxidant	Taniguchi *et al*. (2010)	None available	Prospective, double-blinded, randomized placebo-controlled trial; high dose pirfenidone ($n=108$) *vs*. low dose pirfenidone ($n=55$) *vs*. placebo ($n=104$)	Primary end point: ΔFVC at 52 weeks	Significant reduction in FVC decline in high dose treatment arm. However, change in end point during trial, handling of missing data and absence of patient reported outcome means it is difficult to draw firm conclusions at this time
Pirfenidone	As above	CAPACITY 1 trial (Intermune, USA) Noble *et al*. (2011)	NCT00287729	Prospective, double-blinded, randomized placebo-controlled trial; high dose pirfenidone ($n=171$) *vs*. placebo ($n=173$)	Primary end point: ΔFVC at 72 weeks	Trial completed; no significant difference in FVC decline between treatment groups
Pirfenidone	As above	CAPACITY 2 trial (Intermune, USA) Noble *et al*. (2011)	NCT00287716	Prospective, double-blinded, randomized placebo-controlled trial; high dose pirfenidone ($n=174$) *vs*. low dose pirfenidone ($n=87$) *vs*. placebo ($n=174$)	Primary end point: ΔFVC at 72 weeks	Trial completed; significant reduction in FVC decline in pirfenidone groups

Table 3 (*continued*)

Table 3 (continued)

Agent/ treatment	Potential mechanisms of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/ available	Outcome/comments
Pirfenidone	As above	ASCEND trial (Intermune, USA)	NCT01366209	Prospective, double-blinded, randomized placebo-controlled trial; high dose pirfenidone *vs.* placebo; planned enrollment $n=500$	Primary end point: Δ%FVC at 52 weeks	Trial ongoing; results awaited
GC1008	Anti-TGFβ 1, 2, and 3 antibody	Genzyme and Cambridge Antibody Technology, UK	NCT00125385	Non-randomized, open label, single group assignment Phase I study ($n=25$)	Primary end points: safety and tolerability Secondary end points: potential clinical outcomes up to 3 years	Trial completed; results awaited
STX-100	Anti-αvβ6 integrin	Stromedix, USA	NCT01371305	Phase I studies completed (Stromedix) – awarded orphan drug status (USA) and a Phase II study is ongoing; planned enrollment $n=35$	Primary end point: safety over 24 weeks	Phase I Trial completed; results awaited Phase II Trial ongoing
FG-3019	Connective tissue growth factor inhibitor	Fibrogen, USA	NCT00074698	Open-label Phase I study completed ($n=21$)-awarded orphan drug status (USA); an open-label Phase II study is ongoing ($n=84$)	Phase II trial primary endpoint: safety at 45 weeks Secondary endpoints: effect on extent of pulmonary fibrosis, pulmonary function and dyspnea	Phase I trial completed; FG-3019 is safe and well-tolerated. Future trials will assess therapeutic potential Phase II trial ongoing
Octeotride	Somatostatin analogue	Institut National de la Santé Et de la Recherche Médicale, France	NCT00463983	Non-randomized open label single interventional study with octreotide; ($n=25$)	Monitoring of FVC; DL_{co}; HRCT fibrosis score; 6MWD over 48 weeks	Trial completed; trend of decline in FVC and DICO was lower in subjects treated with octeotride compared to historical, previously published data from other trials

Table 3 (*continued*)

Table 3 (continued)

Agent/treatment	Potential mechanisms of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/available	Outcome/comments
CNTO 888	Anti-CCL2 antibody	Centocor, USA	NCT00786201	Prospective, double-blinded, randomized placebo-controlled Phase II trial; CNTO 888 ± usual therapy *vs*. placebo ± usual therapy; currently recruiting patients, planned total n=120	Primary end points: safety and performance at lung function tests	Trial completed; results awaited
QAX576	Anti-IL-13 antibody; IL-13 stimulates collagen deposition and myofibroblast differentiation	Novartis, Switzerland	NCT00532233	Open label Phase II study (n=50)	Primary end point: IL-13 serum levels Secondary end point: change in designated serum biomarkers over time with treatment for 4 weeks	Trial completed; results awaited
Tralokinumab	Anti-IL-13 antibody; IL-13 stimulates collagen deposition and myofibroblast differentiation	MedImmune LLC.	NCT01629667	Prospective, double-blinded, randomized placebo-controlled Phase II study; high dose tralokinumab *vs*. low dose tralokinumab *vs*. placebo, planned enrollment *n*=186	Primary end point: change from baseline in FVC at week 72 Secondary end point: safety	Trial ongoing
SAR156597	Bispecific Anti-IL-13 and IL-4 antibody; IL-13 stimulates collagen deposition and myofibroblast differentiation; IL-4 promotes fibroproliferation	Sanofi-Aventis	NCT01529853	Prospective, double-blinded, randomized placebo-controlled Phase II study; SAR156597 *vs*. placebo, planned enrollment *n*=24	Primary end point: safety and tolerability over 6 months Secondary end point: change in FVC, DICO and dyspnea score from baseline	Trial ongoing

Table 3 (*continued*)

Table 3 (continued)

Agent/treatment	Potential mechanisms of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/available	Outcome/comments
Thalidomide	anti-angiogenic immunomodulatory anti-inflammatory inhibitor of TGFβ-1 signalling and VEGF expression	Investigator led – John Hopkins University, USA	NCT00162760	Non-randomized open label single interventional study designed for patients who have failed or are unsuitable for immunosuppressive therapy; planned enrollment *n*=19	Primary end point: safety Secondary end points: Δlung function over 1 year	Trial completed; results awaited
GS-6624	Anti-LOXL2 antibody; this enzyme generates crosslinks fibrillar collagen to generate the scaffold on which fibroblasts grow	Gilead Sciences	NCT01362231	Randomized, double-blind, dose escalation study of GS-6624 *vs*. placebo; planned enrollment *n=48*.	Primary end point: safety and tolerability	Phase I trial completed; results awaited Phase II trial planned
BIBF 1120	Angiokinase inhibitor targeting proliferative growth factors in fibroblasts (FGFR, PDGFR, VEGFR)	TOMORROW trial Boehringer Ingelheim Pharmaceuticals, UK	NCT00514683	Prospective, double-blinded, randomized placebo-controlled Phase II study; BIBF1120 *vs*. placebo; total (*n*=400); recruitment complete	Primary end point: ΔFVC over 1 year Secondary end point: dyspnea score, survivial	Trial completed; results awaited
BIBF 1120	As above	INPULSISTM-1 and INPULSISTM-2 trials Boehringer Ingelheim Pharmaceuticals, UK	NCT01335464 and NCT01335477	Prospective, double-blinded, randomized placebo-controlled Phase III studies; BIBF1120 *vs*. placebo; planned enrollment *n*= 515 and 551, respectively.	Primary end point: ΔFVC over 52 weeks	Trials ongoing
Minocycline	Broad spectrum tetracycline with anti-inflammatory and anti-angiogenic properties	Investigator led trial – University of California, USA	NCT00203697	Prospective, double-blinded, randomized placebo-controlled trial; patient numbers not disclosed	Primary end points: safety and efficacy	Trial status unknown; results awaited

Table 3 (*continued*)

Table 3 (continued)

Agent/treatment	Potential mechanisms of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate/available	Outcome/comments
Tetrathiomolybdate	Antiangiogenic	Investigator-led trial – University of Michigan, USA	NCT00189176	Non-randomized, open label, uncontrolled, single group assignment Phase I/II (*n*=20)	Primary end point: safety Secondary end points: Δlung function tests	Trial completed; results awaited
Doxycycline	MMP inhibitor; some MMPs drive cellular apoptosis, migration, proliferation, and angiogenesis	Indian Institute of Chemical Biology, India	None available	Non-randomized, open label, uncontrolled, single group assignment (*n*=6)	Primary end point: inhibition of MMP activity in the BALF at 6 months Secondary end points: ΔFVC, 6MWD, and dyspnea score	Trial completed; a non-statistical trend toward improved 6MWD and FVC
Losartan	Angiotensin II inhibitor	National Cancer Institute, USA	NCT00879879	Open label interventional study; recruiting patients; planned enrollment n=25	Primary end point: FVC response at 1 year	Trial status unknown; results awaited
Carbon Monoxide	Anti-proliferative diatomic gas, inhibitor of fibroblast ECM deposition	Brigham and Women's Hospital, USA	NCT01214187	Prospective, double-blinded randomized placebo-controlled trial; carbon monoxide *vs*. placebo, currently recruiting, planned enrollment n=60	Primary end point: Δserum baseline MMP7 level at 3 months	Trial ongoing
Adjunctive treatment of GER with PPIs or H2 receptor blockers	Gastroesophageal therapy and/or prophylaxis	Lee *et al*. (2011) Raghu *et al*. (2006)	None available	Retrospective case series; PPI or H2 blockers *vs*. no GER therapy; (n=204)	Primary end point: survival from time of IPF diagnosis	Decreased HRCT fibrosis score (14 *vs*. 19%) and improved survival (HR=0.47) in the GER therapy group.
Mesenchymal stem cells	Potential alveolar re-epithelialization	The Prince Charles Hospital, Australia	NCT01385644	Prospective, open-label trial; low dose mesenchymal stem cells (MSC) *vs*. high dose MSC; planned enrollment n=8	Primary end point: safety 6 months post treatment	Trial ongoing

6MWD, 6 min walk test distance; A-a, alveolar:arterial ANZCTR, Australian New Zeland clinical trials registry; BALF, bronchoalveolar lavage fluid; CCL-2, Chemokine (C-C motif) ligand 2; cGMP, cyclic guanosine monophosphate; CRP, clinical-radiographic-physiological; DLco, carbon monoxide dilution; FGFR, fibroblast growth factor receptor; FVC, forced vital capacity; H2, histamine H2 receptor blocker; HRCT, high resolution computer tomography; IFN-γ, interferon-gamma; IL-13, interleukin 13; IL-4, interleukin 4; LOXL-2, lysyl oxidase-like enzyme 2; MMP, matrix metalloproteinase; NCT, clinicaltrials.gov identifier; PDGFR, platelet-derived growth factor receptor; PPI, proton pump inhibitor; pred, predicted QoL, quality of life; TGFβ, transforming growth factor-beta; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Permission has been obtained from John Wiley and Sons for reuse of figure Table 3.

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