Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Clinical trials in idiopathic pulmonary fibrosis: update and perspectives

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Idiopathic pulmonary fibrosis (IPF) is an increasingly prevalent and devastating disease with high mortality and poor treatment options. Major advances in understanding its underlying pathogenesis have changed the traditional concept of IPF being a chronic inflammatory condition to it being a disordered wound healing and repair process, and have enabled the development of novel therapeutic drug strategies. Over the last decade, a number of well-designed clinical trials have been conducted without any tremendous breakthrough to date. Nevertheless, the activities have dramatically improved clinical and basic understanding of IPF and resulted in approval of the first IPF-specific therapy. This review summarizes the most important clinical trials in IPF and outlines both novel drug targets and challenges for future trials.

Keywords: clinical trial • idiopathic pulmonary fibrosis • outcome • pirfenidone • therapy

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease of unknown cause occurring primarily in older adults [1]. It is restricted to the lung and associated with the histopathologic and radiologic pattern of usual interstitial pneumonia (UIP) [1–4]. The diagnosis of IPF requires exclusion of other forms of interstitial pneumonias such as those associated with environmental exposure (e.g., asbestosis or hypersensitivity pneumonia), drugs or connective tissue disease [3]. The incidence is slightly higher for men at 10.7 cases per 100,000 per year, versus 7.4 cases per 100,000 per year for women [5]. Comparing incidence and prevalence data, estimated between 14 and 42.7 per 100,000 [6], median survival is approximately 3 years after diagnosis, which exceeds the mortality rates of many cancers [7]. The dismal prognosis of IPF and lack of efficient therapies highlights the need for new treatment options and explains the current activity in drug development in this area.

Several factors and pathways have been implicated into the pathogenesis of IPF, but the exact pathomechanism has not yet been elucidated, making the development of new therapeutic strategies challenging. Anti-inflammatory and immunomodulatory agents have been used for IPF for years, but have proved to be largely ineffective. This has led to questioning of the concept of an active inflammatory process as a major underlying pathogenetic factor. More recently, IPF has been considered as a primarily fibrotic condition characterized by alveolar epithelial cell injury and aberrant wound healing, resulting in proliferation and migration of mesenchymal cells that accumulate in characteristic fibroblastic foci. Extensive extracellular matrix (ECM) production causes progressive destruction of the lung architecture and eventually respiratory functional impairment, with development of clinical symptoms and death.

The need for new treatment options targeting different pathophysiological pathways has led to a careful evidence-based approach over the past decade with

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completion of a number of high-quality clinical trials. This article provides an overview of historical treatment approaches for IPF and of evidence on therapeutic strategies currently under evaluation, and reviews novel drug targets. The current challenges in designing clinical trials and the need for new outcome parameters are also discussed.

Traditional therapy for IPF: corticosteroids & anti-inflammatory agents

IPF was originally considered as a disorder in which fibrosis was a consequence of chronic inflammatory processes, similar to rheumatoid arthritis. Based on this assumption, corticosteroids and other immunomodulatory agents such as azathioprine and cyclophosphamide were used in the treatment of IPF for several decades. While this was conceptually acceptable at the given time, one has to acknowledge that the use of these drugs was not based on strong scientific evidence and was pursued despite disappointingly poor response rates. It is difficult to interpret the existing evidence of clinical trials with anti-inflammatory agents in IPF. Many studies had been performed before establishing the current guidelines on diagnosis and classification of IPF and likely included patients with heterogeneous causes of interstitial lung disease, which are now known to respond more favorably to immunosuppression [8]. Inconsistent methodology with variable dosage regimen and end points, and the lack of sufficiently powered, placebo-controlled trials, complicate an evidence-based analysis. Of note, this is true for both concluding that immunosuppressant drugs are effective or ineffective for IPF. A thorough analysis of clinical trials exploring the efficacy of corticosteroids for IPF has recently been published in a Cochrane review, concluding that there is no evidence for corticosteroids alone in the treatment of IPF [9]. Interestingly, this analysis did not include clinical trials performed since 2003, which illustrates the expert opinion that corticosteroids are not effective in IPF. Similar conclusions were drawn from a second Cochrane review, focused on nonsteroid agents for IPF. There was one randomized placebo-controlled trial assessing the efficacy of azathioprine versus placebo in combination with prednisone in both arms [10]. In this study, no significant benefit between the groups was found, except a small survival benefit at up to 9 years follow-up after adjustment for age, albeit of questionable clinical significance [10]. There was a trend to improvement in change of lung function with azathioprine. Only one study met the criteria for analysis of cyclophosphamide: Johnson *et al.* compared prednisone alone with cyclophosphamide in combination with low-dose prednisone and found a significantly longer period to respiratory failure or death favoring the treatment arm [11]. Survival was not significantly different and the results were weakened overall by the inclusion of patients that did not meet recent diagnostic criteria of IPF. Cyclosporin A is widely used as an immunosuppressive regimen after transplantation has been investigated in smaller studies, suggesting a possible benefit [12,13], however no randomized placebo-controlled trials have been performed to date. The observation that patients with single lung transplantation who receive a cyclosporine-containing immunosuppressive regimen show progression of IPF in the native lung does not speak in favor of this drug for IPF [14].

Recently completed clinical trials in IPF

IFN-γ

IFN-γ 1b is a cytokine that is predominantly generated by natural killer cells and activated T-helper cells [15]. It has broad immunomodulatory, antifibrotic and antiproliferative properties. IFN-γ has been shown to inhibit fibroblast proliferation and ECM deposition *in vitro* [16,17] and to attenuate bleomycin-induced fibrosis in mouse models [18]. A first study by Ziesche *et al.* reported a significant beneficial effect of IFN-γ in 18 patients with IPF [19] and had been the rationale for initiating the first large clinical trials in IPF. Two randomized, placebo-controlled trials have been performed to assess the efficacy of IFN-γ, but had rather disappointing results. The first study in 330 patients found no significant effect on disease progression, mortality and functional deterioration, but showed a trend towards better survival of the IFN-γ group [20]. This was enough incentive to perform an even larger Phase III multicenter trial enrolling 800 patients (INSPIRE). The study was terminated after an interim analysis demonstrating no difference in mortality [21]. Given this evidence, IFN-γ should not be considered as a suitable treatment for patients with IPF according to the new American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS) guidelines [1].

Etanercept

Etanercept is a recombinant soluble antagonist of human TNF-α being used successfully for the treatment of rheumatoid arthritis and chronic inflammatory bowel disease. TNF-α is a prototypical proinflammatory cytokine and is increased in the lungs of patients with IPF [22–24], especially in macrophages and alveolar epithelial cells. Overexpression of TNF-α in lungs of mice [25] results in accumulation of fibroblasts and deposition of ECM and it has been shown that TNF-α is capable of mediating the transition from inflammation to fibrosis [26]. Animal models of

bleomycin-induced lung fibrosis have shown promising results in attenuating fibrosis by blocking TNF-α. However, a recent randomized double-blind study of etanercept for IPF proved disappointing and failed to affect the outcomes of disease progression and change in the percent of predicted forced vital capacity (FVC) from baseline [27].

Bosentan

Bosentan is an orally available dual endothelin-receptor antagonist developed for the treatment of pulmonary arterial hypertension. Endothelin has strong vasoconstrictory properties and appears to also be involved in the pathogenesis of pulmonary fibrosis by promoting fibroblast proliferation and differentiation into myofibroblasts [28–31], and stimulating collagen synthesis [32]. Elevated levels of endothelin have been found in serum and bronchoalveolar lavage fluid (BALF) of patients with IPF [33]. The effect of bosentan in IPF was evaluated in several appropriately designed trials. The first study (BUILD 1) failed to prove the primary end point of improvement in 6-min walk distance (6MWD), but showed a trend favoring bosentan in respect to time to disease progression and/or death in a subgroup of patients with biopsy-confirmed UIP [34]. These findings triggered a second large clinical trial on bosentan that has recently been published (BUILD 3). In this study, the primary end point of reduction in mortality was not met; however, there was a trend in delay of disease progression and lung function deterioration in favor of the treatment group [35]. Macitentan is a new endothelin-receptor antagonist achieving higher tissue levels and its efficacy in IPF is currently being explored in a clinical trial (MUSIC) [201]. Ambrisentan, another selective endothelin-receptor antagonist, was evaluated in a randomized, double-blind, placebo-controlled trial, which was terminated after an interim analysis due to lack of efficacy [202].

Pirfenidone

Pirfenidone is an orally available pyridine derivative with antifibrotic, anti-inflammatory and antioxidative properties. The exact molecular mechanism of this drug is still unclear, but it has been shown to inhibit TGF-β-driven fibroblast proliferation and collagen synthesis *in vivo* [36,37]. It also has some anti-inflammatory properties related to attenuation of TNF-α and IFN-γ activity [38–40]. Promising results from animal models and smaller, open-label clinical studies [41,42] have provided the rationale to perform a number of large clinical trials. The first study was performed in Japan and had to be stopped prematurely because of a positive effect on disease exacerbations in favor of pirfenidone [43]. Although this study was incomplete, the decreasing oxygen desaturation (6MWD test) and vital capacity (VC) in the treatment group was lower compared with placebo. The following Phase III study reported a significant reduction in the annual decline of vital capacity and a difference in progression-free survival in favor of pirfenidone [44]. Two parallel, randomized, double-blind, placebo-controlled multicenter studies were performed to reproduce the effects of pirfenidone on reduction of FVC decline (CAPACITY I and II) [45]. The first of these studies reached the primary end point of change in predicted FVC at week 72 favoring the treatment arm. In contrast, the second study did not meet the primary end point although a significant change in the percentage predicted FVC was observed at all time points during the first year [45]. Overall, the results from the CAPACITY studies were consistent compared with the Phase III Japanese trial [44,45]. The difference in the FVC outcome between CAPACITY 1 and 2 may partially be related to the lower than expected decline in FVC. While the pirfenidone arm in both studies showed a similar magnitude of decline in %FVC over 72 weeks, the decline in the placebo arms differed between the studies. The percentage predicted FVC decline in the placebo arm of the 'positive' CAPACITY 2 study was similar to the placebo group of the large IFN-γ trial, whereas the placebo arm of the 'negative' CAPACITY 1 performed better than expected from past experience. This supported the hypothesis that the placebo group of the second study included patients with a more stable course of disease. A survival benefit was not established for all-cause on-treatment mortality, and pirfenidone did not prevent acute exacerbations of IPF [45]. The pirfenidone data has also been reviewed in a recent Cochrane meta-analysis, even prior to the publication of the CAPACITY trials, suggesting an overall benefit for pirfenidone over placebo (the authors had access to the CAPACITY data for their analysis) [46].

In summary, the results from preclinical and clinical studies regarding pirfenidone look encouraging, but include some inconsistencies and findings that are difficult to explain. One of these is that the natural course of patients with IPF at a relatively early stage may not be as easily predictable as hoped, as seen by the (unexpected) relative stability of IPF in CAPACITY 1. Nevertheless, the efforts have led to approval of this compound as the first IPF-specific therapy in Japan (2008) and Europe (2011) [47], while approval has not been granted by the US FDA in the USA, where another Phase III trial is currently underway [203]. The recently published ATS/ERS/JRS guidelines have summarized the pirfenidone data to date as 'weak – no recommendation for use in IPF'. By looking into

the details of the guideline panel process, one can see that the experts are more divided in their interpretation of the pirfenidone data than for other drugs [1]. Pirfenidone seems to be a safe and reasonably well tolerated medication, but is associated with gastrointestinal side effects, liver enzyme elevation and significant photosensitivity [45]. It will be very interesting to see the impact of pirfenidone in clinical practice and if/how it might change the management and outcome of IPF patients.

■ Imatinib

Imatinib is a tyrosine kinase inhibitor (TKI) developed as an anticancer drug and successfully used in the treatment of chronic myelogenous leukemia. With its activity against platelet-derived growth factor receptors (PDGFR) suggested as being one of the biologically relevant pathway in fibrosis, it is reasonable to assume antiproliferative and antifibrotic properties for imatinib in IPF. Studies of imatinib in preclinical animal models have shown mixed results [48–51], but imatinib seems to have the ability to ameliorate bleomycin-induced fibrosis by inhibition of downstream TGF-β pathways when given early [49]. In contrast, when administered during the post-injury phase, imatinib has failed to alter fibrotic changes in the lungs [51]. A well-designed, multicenter, randomized, placebo-controlled clinical trial over 96 weeks on patients with mild-to-moderate IPF failed to prove a benefit on progression-free survival and lung function [52].

■ *N*-acetylcysteine

N-aetylcysteine (NAC) is a derivative of the amino acid cysteine and a precursor of the antioxidant glutathione. The rationale for NAC in the therapy of IPF is based on a putative imbalance of oxidant–antioxidant components in inflammatory and fibrotic tissue. We have recently shown that fibrogenic cytokines such as TGF-β are constantly activated in fibrotic lungs and that replenishment of the antioxidative system is antifibrotic through reduction of active growth factor levels [53]. Glutathione levels are reduced in tissue and BALF of IPF lungs [54,55] and can be normalized by oral NAC [56]. The IFIGENIA trial assessed the effect of high-dose NAC versus placebo in IPF patients receiving combination therapy of prednisone and azathioprine. The 12-month decline in FVC and diffusing capacity of the lung for carbon monoxide (DL_{CO}) were significantly reduced in the NAC arm, without a resulting survival benefit during the study period (9% NAC vs 11% placebo) [57,58]. In this study the combination of NAC plus azathioprine plus prednisone is widely used for IPF, although the recent ATS/ERS/JRS guidelines on IPF summarized the evidence regarding this therapy with a 'weak recommendation' against its use [1]. The major limitations of IFIGENIA were a relatively large dropout rate, the unclear clinical significance of the treatment effect and the fact that there was no true placebo arm. For that reason, a multicentered, randomized, double-blind clinical trial assessing the efficacy of prednisone, azathioprine and NAC compared with NAC alone and compared with placebo is currently underway under the direction of the NIH-sponsored IPF network [204]. Recently, one arm of this study has been stopped after an interim analysis showed that patients receiving prednisone, azathioprine and NAC had greater mortality, more hospitalizations, more serious adverse events and no changes in lung function. The other two study arms, NAC alone and placebo alone will continue [205].

■ Anticoagulants

Anticoagulants have also been investigated as anti-IPF drugs. It has been shown that the coagulation cascade is highly active in IPF lungs, for example with increased expression of tissue factor in alveolar epithelium [59] and increased levels of thrombin in the BALF [60]. Scotton *et al.* recently reported increased expression of coagulation Factor X in the intra-alveolar compartment of IPF tissue and in the lungs of bleomycin-induced pulmonary fibrosis [61]. There seems to be a central role for the high-affinity thrombin receptor, PAR-1 [62], which is expressed on fibroblast, epithelial cells and macrophages. Activation of this receptor leads to increased release of proinflammatory and profibrotic cytokines, such as PDGF and CTGF, by fibroblasts [63,64], and PAR-1 signaling in fibroblast promotes differentiation into myofibroblasts via the TGF-β pathway [61]. Anticoagulants have been shown to be effective in attenuating fibrosis in experimental animal models [61,65,66]. Given the preclinical data, therapeutic anticoagulation with low-molecular-weight heparin and warfarin has been evaluated in combination with prednisone in a small clinical trial in Japan [67]. The study showed a significant difference in overall survival favoring the treatment arm, and the frequency of acute exacerbations was significantly reduced. While these results look encouraging, there were major methodological limitations with this study, including the absence of blinding, lack of a true placebo arm, varying dropout rates, inconsistent diagnostic criteria and the lack of exclusion of pulmonary embolism as a potential cause of deterioration. The NIH-sponsored IPF network conducted a properly designed study to investigate the effect of anticoagulants in IPF (ACE-IPF [206]), which was recently terminated due to lack of efficacy after an interim analysis.

Sildenafil

Sildenafil is an oral phosphodiesterase-5 inhibitor that is approved for the treatment of pulmonary arterial hypertension. It stabilizes CGMP, a second messenger of nitric oxide, and leads to pulmonary vasodilatation predominantly in well-ventilated areas of the lung. Patients with severe IPF and a markedly reduced DL_{CO} frequently develop pulmonary vascular disease with pulmonary hypertension [68]. Systemic vasodilatation can increase blood flow into poorly ventilated areas of the IPF lung by interacting with the physiological hypoxic vasoconstrictor mechanism, thereby decreasing shunt flow and gas exchange [69,70]. Avoiding increased shunt flow by lung-selective and 'supra-selective' vasodilator (active only in well-ventilated and not whole lung) could improve ventilation–perfusion mismatching and gas exchange in IPF [71]. Sildenafil has shown some promise after a few small cohort studies reported an improvement in exercise tolerance, a reduced degree of dyspnea and quality of life (QOL) in patients with advanced IPF [72,73]. These observations were the initiator for another NIH-sponsored IPF network trial (STEP-IPF) that evaluated sildenafil in patients with IPF and severely reduced DL_{CO}. The study failed to prove the primary end point of 20% change in 6MWD at 12 weeks, but showed significant effects on secondary end points, including dyspnea, DL_{CO}, partial pressure of oxygen and QOL favoring sildenafil [74]. The association of symptomatic improvement with sildenafil may be of value to patients with advanced fibrosis, but further studies are required to obtain conclusive evidence.

Supplementary Table 1 provides a summary of recently published and completed, but not yet published clinical trials that followed the current ATS/ERS diagnostic criteria for IPF.

Ongoing clinical trials & future drug targets

The improved understanding of the pathogenesis underlying IPF resulted in a number of novel drug targets with high activity in preclinical and clinical research. Many of the agents tested in those studies are aimed at upregulated mechanisms in the fibrotic process of IPF, including inhibition of growth factors, cytokines and signaling pathways. The extensive research over the past decade clearly demonstrated that there is a significant redundancy of the underlying pathways involved in wound repair and fibrosis. Therefore, targeting more than one ligand–receptor interaction seems to be a reasonable approach for development of new treatment options. As already discussed, the TKI imatinib, which blocks PDGF via the c-abl tyrosine kinase, did not prove to be effective in IPF. The molecule BIBF 1120 is a newer TKI, originally developed as an anti-angiogenic drug for cancer treatment. It blocks tyrosine kinase signaling by inhibiting VEGFR, FGFR and PDGFR, each of which is involved in fibrogenesis. This approach was able to reduce bleomycin-induced lung fibrosis, notably not only at the time of injury in a preventative model, but also in a genuinely therapeutic manner when fibrosis was present [75]. The results of a multicenter, randomized, placebo-controlled trial designed to evaluate safety and efficacy of oral BIBF1120 on decline in FVC in patients with IPF have recently been published. The data suggest that BIBF1120 may be able to reduce lung function decline in IPF and was also associated with fewer acute exacerbations similar to those that have been reported for pirfenidone [76]. The compound also had a positive impact on QOL as assessed by the St George's Respiratory Questionnaire [76].

Several new and promising approaches are targeting the redox equilibrium, the ECM homeostasis and the coagulation cascade. As already mentioned, the results from the IFIGENIA trial [57] provided some stimulus to investigate the oxidant–antioxidant imbalance in IPF in-depth. NOX-4 is an enzyme that catalyzes the reduction of O_2 to reactive oxygen species and targeting this pathway was shown to ameliorate fibrosis by interfering with TGF-β-induced myofibroblast differentiation [77,78]. Laleu *et al.* developed a new class of selective and orally available NOX-4 inhibitors as new treatments for IPF, which might have the potential for evaluation in clinical trials [79].

The excessive accumulation of ECM is a key phenomenon in the pathogenesis of IPF and targeting the complex pathways involved in ECM synthesis, maturation and degradation seems to be a promising approach for treatment. LOXL-2 belongs to a family of five enzymes containing an extracellular copper-dependent amine oxidase that modulates the formation of ECM by catalyzing the crosslinking of fibrillar collagen I and elastin [80]. LOXL-2 expression has been implicated in tumor biology and liver fibrosis with a possible role in promoting cancer invasion [81–83]. It has also been shown that LOXL-2 is upregulated in human IPF tissue [84]. Targeting LOXL-2 with an allosteric, monoclonal antibody AB0023 markedly improved fibrosis in the bleomycin model, with a significant reduction of activated fibroblasts and crosslinked fibrillar collagens, decreased production of growth factors, cytokines and TGF-β pathway signaling [84]. LOXL-2 expression is relatively low in normal tissue so that targeting this mechanism seems a very promising and encouraging way for the development of new therapeutic interventions. A Phase I dose-escalating study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of

AB0024 in IPF has recently been registered and will be one of the most interesting to follow due to the unique approach that it takes, targeting mature and not newly synthesized collagen [207].

Myofibroblasts are key effector cells in the fibrotic process and as such obvious targets in IPF drug development. Proliferation of resident fibroblasts and epithelial–mesenchymal transition are potential sources for myofibroblasts. Recent evidence has also suggested that the recruitment of fibrocytes (mesenchymal cell progenitors) from the circulation may be a contributing factor to the increased presence of myofibroblasts in fibrotic lungs [85]. The short pentaxin SAP is a circulating protein belonging to the acute-phase proteins. It binds to apoptotic cells, clears cellular debris [86–88] and affects remodeling processes in a variety of organs [89–91]. It has gained some interest since it has been shown to inhibit fibrosis in a number of preclinical disease models through inhibition of peripheral blood mononuclear cells (and fibrocytes) [90,92,93]. Its antifibrotic effects are mediated through Fcγ receptors, which affect monocyte differentiation and activation [88,89]. Murray *et al.* described a reduction of bleomycin-induced lung fibrosis in mice by SAP through inhibition of macrophage accumulation in the lung [94]. They later showed in a mouse model of chronic TGF-β1 overexpression that SAP inhibits TGF-β driven pathologies, including epithelial apoptosis, airway inflammation, macrophage activity, fibrocyte accumulation and collagen deposition by interfering with TGF-β activation, without affecting the actual levels of TGF-β1 [95]. SAP is already in a Phase I clinical trial [208]. Recent ongoing clinical trials are summarized in Supplementary Table 2.

Challenges to drug development & trial design in IPF

The design and development of novel drugs and clinical trials in IPF remains difficult and challenging for several reasons:

- Despite considerable progress in understanding the underlying mechanisms involved in the fibroproliferative process, many unanswered questions remain. The complex interplay of cellular and signaling mechanisms will most likely require a multitargeting approach and combination therapy, with compounds that could be used in parallel or sequentially. It is plausible that the relative role of the different pathogenetic pathways involved varies across individuals, highlighting the need for identifying subgroups of phenotypes that are more likely to respond to a given drug regimen;

- The natural history and intrinsic behavior of IPF is usually unpredictable, varying between slow progression, frequent exacerbations, and rather dramatic and rapid worsening with respiratory failure (Figure 1) [1,96]. The heterogeneity in disease progression makes recruiting the right patients for clinical trials challenging, as seen in the CAPACYTY trial [45] where the placebo group in one of the two trials contained more stable patients than would have been expected from past clinical trials;

- Animal models have proven helpful in identifying molecules and cells involved in the fibrotic process in IPF. However, preclinical drug development still suffers from the fact that there are no good models that mimic all pathologic changes seen in IPF, they only show certain features of the disease. For example, the bleomycin model is inexpensive, well-established, well-characterized and widely used in preclinical studies in pulmonary fibrosis [97], but it has far more often failed to provide convincing correlative preclinical

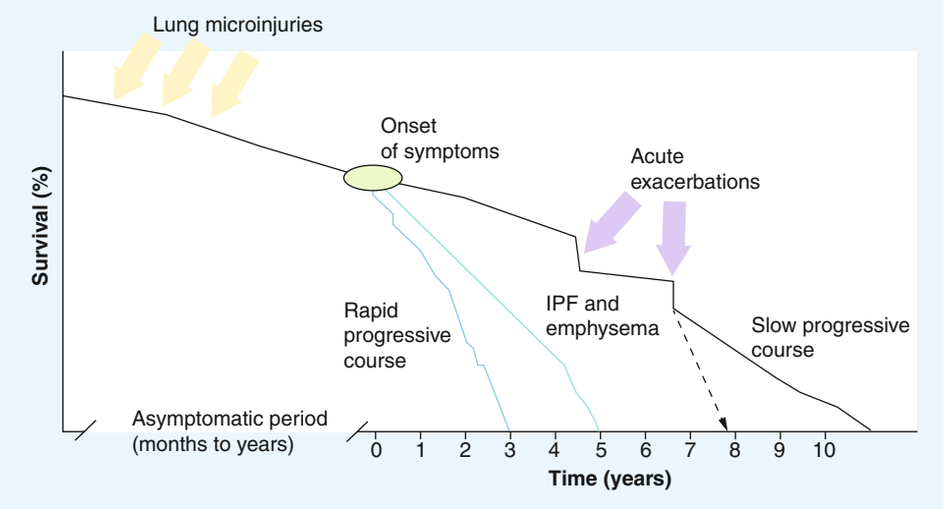

Figure 1. Clinical phenotypes of idiopathic pulmonary fibrosis. The majority of patients experience a slow but steady clinical and functional decline (slow progressive) after diagnosis. Approximately 10% of these patients present with acute exacerbations. A minority of patients may experience a rapidly progressive clinical course while patients with IPF and emphysema due to cigarette smoke have a shorter survival compared with IPF patients alone.
IPF: Idiopathic pulmonary fibrosis.
Reproduced with permission from [96].

data for new therapeutic interventions than it has been successful. Most drugs that have been proposed to be 'promising' for the treatment of IPF following successful intervention in the bleomycin model have not held up to their promise after evaluation in the clinical setting [98]. Some exceptions may finally become true for pirfenidone and BIBF 1120. Furthermore, drug intervention studies in the bleomycin model using a preventive strategy are difficult to translate to the natural scenario of human disease since patients present with established fibrosis [98]. Developing a model that reflects the features and developmental process of UIP would provide a powerful tool for further drug development in this devastating disease, but is still far from reality;

- One of the most demanding issues in designing clinical trials in IPF is choosing the appropriate outcome parameters as end points allowing statistical assessment of clinically meaningful effects. Looking at the clinical trial activity of the past 10 years, one has to notice a lack of consensus about the best end points. This inconsistency poses a slight problem in comparing the trials and their results. While impact on mortality in a fatal disease, such as IPF, is in theory the best outcome, it is not feasible to perform such trials as they would need to be either too long or require too many patient numbers. **Box 1** demonstrates the heterogeneity of outcomes used in recent trials. Meaningful clinical end points have to be reliable, valid, responsive to changes in disease status and treatment effects and, furthermore, be predictive of clinical outcome. FVC is the most widely used and accepted end point to assess disease status in patients with IPF [3]. Recent data have shown that when FVC was assessed for reliability, validity and responsiveness to disease changes it correlates with other functional parameters including DL_{CO}, QOL and dyspnea, thus representing a clinically useful measure for disease status and valid end point for clinical trials [99]. The last few trials have suggested that a 10% decline in FVC over 1 year may be an appropriate surrogate for disease progression and increased risk of mortality [100–102]. Therefore, most trials nowadays use the potential effect of a drug on reducing the 10% FVC annual decline as a primary end point. Recent work suggests that even smaller changes may be of clinical significance in IPF patients [103,99]. The 6MWD test is an inexpensive and practical test to assess the exercise capacity in IPF and is widely used as an end point in pulmonary arterial hypertension [104]. The suitability of the 6MWD as a surrogate marker in patients with IPF was assessed similar to FVC using data from the large INSPIRE trial and revealed that it is a reliable, valid and responsive measure of disease status and may be a reasonable end point for clinical trials [105]. However, patients with severe physiologic impairment were excluded from this trial and patients with advanced disease might not be able to complete a full walk test. Besides FVC [8,102,106,107] and 6MWD test [105,108,109], a number of other end points have been suggested to be predictive for mortality, including DL_{CO} [101,106,107], alveolar–arterial gradient [8,106], 6MWD test desaturation [110], high-resolution computed tomography fibrosis score [111], dyspnea [8] and biomarkers such as circulating fibrocytes [112] or CCL18 [113]. Since there is increasing awareness about parallels in biology and clinical course between IPF and cancer, the primary end point of progression-free survival, which is usually assessed in cancer trials, may be a potentially suitable end point for IPF as well as QOL.

Box 1. Primary end points of clinical trials in idiopathic pulmonary fibrosis.

- Pirfenidone
  - Noble *et al.* [45] FVC
  - Taniguchi *et al.* [44] VC
  - Azuma *et al.* [43] 6MWD, $P(Aa)O_2$
- Interferon
  - Raguh *et al.* [20] PFS†
  - King *et al.* [21] Survival
- Etanercept
  - Raguh *et al.* [27] FVC, DL_{CO}, $P(Aa)O_2$
- Bosentan
  - King *et al.* [34] 6MWD
  - King *et al.* [35] Survival
- NAC
  - Demedts *et al.* [57] VC, DL_{CO}
- Anticoagulant
  - Kubo *et al.* [67] Survival
- Sildenafil
  - Zisman *et al.* [74] 6MWD
- BIBF 1120
  - Richeldi *et al.* [76] FVC
- Imatinib
  - Daniels *et al.* [52] PFS‡

†More than 10% decline from baseline of predicted VC or an increase 5 mmHg in the alveolar–arterial oxygen tension difference at rest.
‡Time to disease progression defined as decline in FVC (%) from baseline predicted FVC or death.
6MWD: 6-min walk distance; DL_{CO}: Diffusing capacity of the lung for carbon monoxide; FVC: Forced vital capacity; $P(Aa)O_2$: Alveolar-arterial oxygen tension difference; PFS: Progression-free survival; VC: Vital capacity.

Future perspective

IPF is an increasingly prevalent and devastating disease with high mortality rates and poor treatment

options. Major advances in understanding its underlying pathogenesis have changed the traditional concept of IPF being a chronic inflammatory condition to it being a disordered wound healing and repair process, and have enabled the development of novel therapeutic drug strategies. Over the past decade a number of well-designed clinical trials have been conducted, without a tremendous breakthrough to date. However, the clinical research has dramatically enhanced the existing knowledge about IPF, which resulted in the first evidence-based guideline on diagnosis and clinical management of IPF. While this document, edited by several of the major international respiratory societies, provides detailed algorithms on the required diagnostic steps and has strong recommendations against certain therapies (e.g., prednisone monotherapy, interferon and bosentan), it remains relatively vague in its statement on the newer and more promising medical treatments [1]. Nevertheless, the recent approval of a first IPF-specific drug, pirfenidone, has to be seen as a major stepping-stone in the management of IPF, although not necessarily because of its efficacy, which some consider marginal despite being statistically significant. The approval will hopefully encourage clinicians and basic scientists, industry and patients that with further collaboration there is a light at the end of the tunnel and improving outcomes, QOL and survival in this devastating disease may finally be within reach. Based on the complexity of IPF, a profoundly successful treatment strategy will eventually require combination therapy targeting multiple pathways. The clinical trial activity of the past 10 years did not only help to improve our understanding of IPF and its natural progression, it also allowed the determination of a solid outcome for future trials, such as FVC decline of 10%, or maybe even less. Finally, the joint efforts in IPF drug development have formed a close collaborative interplay between academic institutions, international clinical networks and the pharmaceutical industry, which will be a major bonus for the coming years and, hopefully, result in much improved medication for IPF patients.

Supplementary data

Supplementary data accompanies this paper and can be found at www.future-science.com/doi/suppl/10.4155/CLI.11.155

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Executive summary

- Major advances in understanding the underlying pathogenesis have changed the traditional concept away from idiopathic pulmonary fibrosis (IPF) being a chronic inflammatory condition to a disordered wound healing and repair process; this has enabled the development of novel therapeutic drug strategies.
- The need for new treatment options targeting different pathophysiological pathways has led to a careful evidence-based approach in IPF over the past decade with a number of high-quality clinical trials.
- To date, no scientific breakthrough has been achieved despite encouraging developments.
- The clinical trial activity has improved basic and clinical understanding of IPF and resulted in the first evidence-based guideline on diagnosis and clinical management.
- Based on the scientific evidence there is a strong recommendation against the use of prednisone monotherapy or in combination with immunomodulatory agents, IFN-γ, etanercept and bosentan.
- The clinical trial activity resulted in the recent approval of the first IPF-specific drug pirfenidone in Europe and Japan.
- It can be expected that the approval of pirfenidone will encourage clinical scientists and industry to further research, however, the impact of pirfenidone in clinical practice and management has to be established.
- Based on the complexity of IPF, we speculate that a successful treatment strategy will eventually require combination therapy targeting multiple pathways.
- The unpredictable natural history of IPF with its heterogeneity in disease progressing is a challenge for the clinical trial design and recruitment of appropriate patients. Identifying different phenotypes that are more likely to respond to a given drug regimen might improve clinical trial outcomes.
- New animal models reflecting the features and developmental process of usual interstitial pneumonia are required for further drug development.
- The clinical trial activity over the past decade suggested forced vital capacity decline of 10% or even less as solid outcome for future trials.
- With further collaboration between clinicians, basic scientists, industry and patients it can be anticipated that further drug development will result in much improved outcomes, quality of life and survival in this devastating disease.

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