



Idiopathic pulmonary fibrosis: lessons from clinical trials over the past 25 years

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Clinical trials in IPF have transformed our understanding of how this devastating disease should be treated <http://ow.ly/47IM30eX5Pr>

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ABSTRACT Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal disease. A major breakthrough in treatment came when, after decades of clinical trials which failed to identify an efficacious treatment regimen, two therapies were successful in Phase-III trials. The advent of these therapies, nintedanib and pirfenidone, meant that for the first time IPF patients had two treatment options that could reduce disease progression. This review summarises the key lessons to be obtained from the clinical trials that led to the current international clinical practice guidelines for the treatment of IPF and provides insights for the design of future clinical trials that are needed if we are to improve outcomes that are clinically meaningful to IPF patients.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a fibrotic lung disease characterised by worsening dyspnoea and progressive loss of lung function [1, 2]. Data from a large insurance claims database in the United States suggests that the incidence of IPF among people aged 18–64 years between 2005 and 2010 was 6.1 new cases per 100 000 person–years [3]. IPF primarily affects older individuals, with a median age at diagnosis of 66 years [4]. The clinical course of IPF is variable and largely unpredictable. Some patients experience periods of stability followed by acute deteriorations in lung function known as acute exacerbations [5]. IPF is ultimately fatal, with historical data suggesting a median survival time of 2–3 years from diagnosis; however, post-diagnosis survival time is likely to increase as patients are diagnosed earlier in the course of the disease [6].

A decline in forced vital capacity (FVC) is indicative of disease progression in patients with IPF and change in FVC is the most commonly used endpoint in clinical trials [7, 8]. A decline in FVC of 5% or 10% of the predicted value over 6–12 months has been associated with increased mortality in patients with IPF [7, 9, 10]. Furthermore, using relative rather than absolute change in FVC as an endpoint may increase the chance of identifying a clinically relevant decline in FVC [11].

Our understanding of the pathogenesis of IPF has evolved from that of a predominantly inflammatory disease to one driven by a complex interplay of repeated epithelial cell damage and aberrant wound healing, involving fibroblast recruitment, proliferation and differentiation, and culminating in excess deposition of extracellular matrix [12]. This shift in knowledge prompted a change in the type of compounds being investigated as potential therapies, with those targeted at specific pathways in the development and progression of fibrosis becoming the focus. However, several target compounds that had biological plausibility and were effective in preclinical models of pulmonary fibrosis did not improve outcomes when tested in clinical trials.

Over the past 25 years there have been numerous Phase-II or Phase-III randomised, double-blind controlled trials of potential therapies for IPF (figure 1). Most of these trials failed to demonstrate the effectiveness of the compound under investigation (table 1) but they generated a wealth of data to inform the design of future trials. Two antifibrotic drugs, nintedanib and pirfenidone, have now shown efficacy in Phase-III clinical trials, have been approved for the treatment of IPF and have transformed the therapeutic options available to patients [34]. In this review, the key findings from clinical trials in IPF over the past

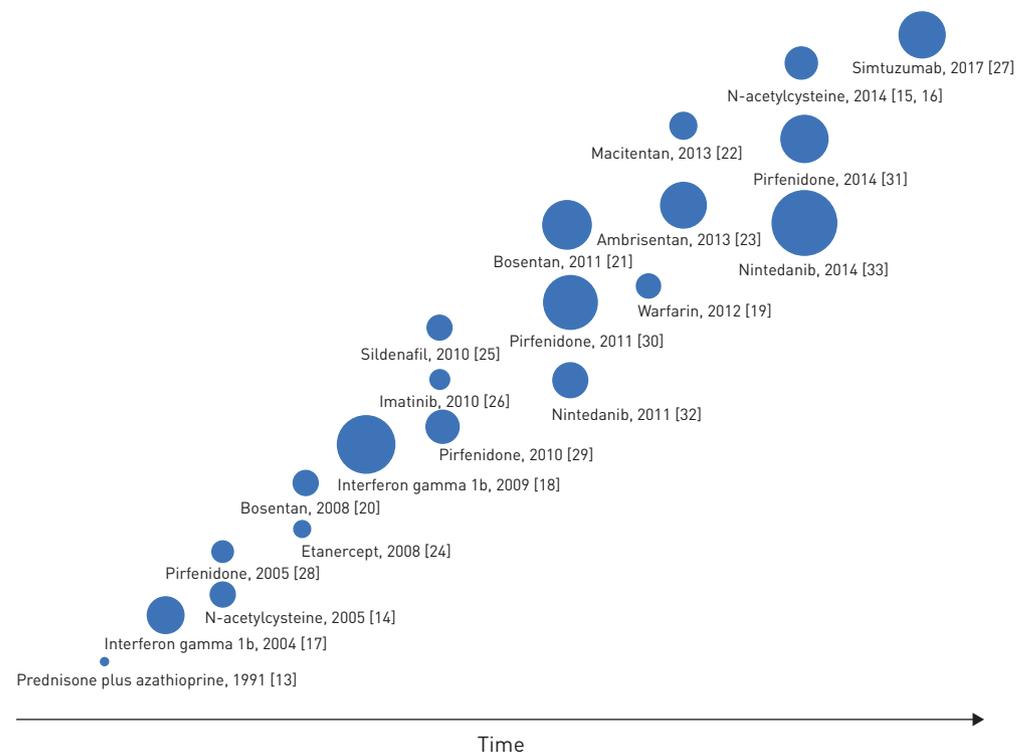


FIGURE 1 Schematic illustration of the published reports of prospective, double-blind, randomised clinical trials over the past 25 years (the time axis is not linear). The size of the spot corresponds to the sample size of the clinical trial.

TABLE 1 Overview of Phase-II and Phase-III trials of investigational treatments for idiopathic pulmonary fibrosis (IPF)

Study name	Treatment 1	Treatment 2	Study design	Primary endpoint(s)	Results
IFIGENIA [14]	Prednisone + azathioprine + NAC (n=80)	Prednisone + azathioprine (n=75)	Phase-III, randomised	Change in VC and DLco from baseline at month 12	Significant benefits from triple therapy were demonstrated for both endpoints Absolute between-group differences for mean change from baseline in VC and DLco at month 12 were 0.18 L (95% CI: 0.03–0.32; p=0.02) and 0.75 mmol·min ⁻¹ ·kPa ⁻¹ (95% CI: 0.27–1.23; p=0.003), respectively
PANTHER-IPF [15]	NAC + prednisone + azathioprine (n=77) [#]	Placebo (n=131)	Phase-III, randomised	Change in FVC from baseline at week 60	The NAC + prednisone + azathioprine arm was terminated due to an increased rate of death and hospitalisation <i>versus</i> a placebo
PANTHER-IPF [16]	NAC (n=133)	Placebo (n=131)	Phase-III, randomised	Change in FVC from baseline at week 60	No significant difference was observed between NAC and a placebo for the primary endpoint (mean changes in FVC of –0.18 L and –0.19 L, respectively; p=0.77)
Interferon gamma-1b trial [17]	Interferon gamma-1b (n=162)	Placebo (n=168)	Phase-III, randomised	Time to disease progression (decline in FVC ≥10% of predicted or increase in P(A-a)O ₂ of ≥5 mmHg at rest) or death	No significant difference was observed between interferon gamma-1b and a placebo for the primary endpoint (median of 439 and 344 days, respectively; p=0.5)
INSPIRE [18]	Interferon gamma-1b (n=551)	Placebo (n=275)	Phase-III, randomised	Survival	Trial was terminated when an interim analysis showed no significant difference between interferon gamma-1b and a placebo for the primary endpoint (HR 1.15; 95% CI: 0.77–1.71; p=0.50)
ACE-IPF [19]	Warfarin (n=72)	Placebo (n=73)	Phase-III, randomised	Composite of time to death, hospitalisation (non-bleeding, non-elective), or absolute decline in FVC ≥10% of predicted	Trial terminated after mean follow-up of 28 weeks, when interim analysis showed higher mortality with warfarin <i>versus</i> a placebo (14 deaths <i>versus</i> 3 deaths; p=0.005)
BUILD-1 [20]	Bosentan (n=74)	Placebo (n=84)	Phase-III, randomised	Change in 6-MWD from baseline at month 12	No significant difference was observed between bosentan and a placebo for the primary endpoint (mean changes of –52 m and –34 m, respectively; p=0.23)
BUILD-3 [21]	Bosentan (n=407)	Placebo (n=209)	Phase-III, randomised	Time to worsening of IPF (decline in FVC ≥10% of predicted and decline in DLco ≥15% of predicted, or acute exacerbation) or death	No significant difference was observed between bosentan and a placebo for the primary endpoint (HR 0.85; 95% CI: 0.66–1.10; p=0.21)
MUSIC [22]	Macitentan (n=119)	Placebo (n=59)	Phase-II, randomised	Change in FVC from baseline at month 12	No significant difference was observed between macitentan and a placebo for the primary endpoint (median change of –0.20 L in both groups)
ARTEMIS-IPF [23]	Ambrisentan (n=329)	Placebo (n=163)	Phase-III, randomised	Time to disease progression (defined as death, respiratory hospitalisation, or categorical decline in lung function (FVC ≥10% of predicted plus DLco ≥5% of predicted, or FVC ≥5% of predicted plus DLco ≥15% of predicted) (event-driven)	Trial terminated after interim analysis showed a low likelihood of demonstrating efficacy on the primary endpoint
Etanercept trial [24]	Etanercept (n=46)	Placebo (n=41)	Phase-II, randomised	Changes in FVC (% predicted), DLco (% predicted), and P(A-a)O ₂ (at rest) from baseline at week 48	No significant differences were observed between etanercept and a placebo for the lung function endpoints

Continued

TABLE 1 Continued

Study name	Treatment 1	Treatment 2	Study design	Primary endpoint(s)	Results
STEP-IPF [25]	Sildenafil (n=89)	Placebo (n=91)	Phase-III, randomised for 12 weeks followed by 12-week open-label extension	≥20% increase in 6-MWD at week 12	No significant difference was observed between sildenafil and a placebo on the primary endpoint (10% and 7% of patients, respectively; p=0.39)
Imatinib trial [26]	Imatinib (n=59)	Placebo (n=60)	Phase-II, randomised for 96 weeks	Time to disease progression (defined as decline in FVC from baseline of >10% of predicted) or death	No significant difference was observed between imatinib and a placebo on the primary endpoint (HR 1.05; 95% CI: 0.56–1.96; p=0.89)
Simtuzumab trial [27]	Simtuzumab (n=272)	Placebo (n=272)	Phase-II, randomised	Progression-free survival (defined as death or a categorical decline in FVC (% predicted) from baseline, <i>i.e.</i> ≥10% relative decline and ≥5% absolute decline)	Trial was terminated when interim analysis showed no significant difference between simtuzumab and a placebo on progression-free survival (HR 1.13; 95% CI: 0.88–1.45; p=0.33)
Pirfenidone trial [28]	Pirfenidone (n=72) [¶]	Placebo (n= 35)	Phase-II, randomised, in Japanese patients	Change from baseline in lowest SpO ₂ during a 6-min steady-state exercise test at month 6	Trial terminated when interim analysis showed no significant difference between pirfenidone and a placebo for the primary endpoint at month 6 (increase of 0.64% <i>versus</i> decrease of 0.55%, respectively; p=0.15)
Pirfenidone trial [29]	Pirfenidone (n=55-108) [*]	Placebo (n=104)	Phase-III, randomised in Japanese patients	Original: change from baseline in lowest SpO ₂ during a 6-min steady-state exercise test at week 52 Revised: change in VC from baseline at week 52	Significant benefits were seen with high-dose pirfenidone <i>versus</i> a placebo for change in VC at week 52 (–0.09 L <i>versus</i> –0.16 L; p=0.0416)
CAPACITY [30]	Pirfenidone (n=87–345) [§]	Placebo (n=347)	Phase-III, randomised (two trials)	Change in FVC (% predicted) from baseline at week 72	Significant benefits were observed with pirfenidone (dose: 2403 mg·day ^{–1}) <i>versus</i> a placebo for the primary endpoint in CAPACITY-2 (–8.0% <i>versus</i> –12.4%; p=0.001) but not in CAPACITY-1 (–9.0% <i>versus</i> –9.6%, respectively; p=0.50)
ASCEND [31]	Pirfenidone (n=278) ^f	Placebo (n=277)	Phase-III, randomised	Change in FVC (% predicted) from baseline at week 52	Significant benefits were observed for pirfenidone <i>versus</i> a placebo for the primary endpoint (p<0.001)
TOMORROW [32]	Nintedanib (n=85–86) ^{##}	Placebo (n=85)	Phase-II, randomised	Annual rate of decline in FVC	Reduced FVC decline with nintedanib (150 mg twice daily) <i>versus</i> a placebo (–0.06 L <i>versus</i> –0.19 L; p=0.06 with closed testing procedure; p=0.01 with hierarchical testing procedure)
INPULSIS [33]	Nintedanib (n=638) ^{¶¶}	Placebo (n=423)	Phase-III, randomised (two trials)	Annual rate of decline in FVC	Significant benefits were observed for nintedanib <i>versus</i> a placebo for the primary endpoint in INPULSIS-1 (–114.7 mL <i>versus</i> –239.9 mL; p<0.001) and INPULSIS-2 (–113.6 mL <i>versus</i> –207.3 mL; p<0.001)

NAC: N-acetylcysteine; VC: vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; HR: hazard ratio; P(A-a)O₂: alveolar to arterial oxygen pressure difference; 6-MWD: 6-min walk distance; SpO₂: arterial oxygen saturation measured by pulse oximetry. [#]: compared with NAC (n=81) and placebo (n=78); [¶]: 200–600 mg (three times daily); ^{*}: pirfenidone dose: high (n=108), low (n=55); [§]: pirfenidone dose: 1197 mg·day^{–1} (n=87), 2403 mg·day^{–1} (n=345); ^f: pirfenidone dose: 2403 mg·day^{–1}; ^{##}: nintedanib dose: 50 mg once daily (n=86), 50 mg twice daily (n=86), 100 mg twice daily (n=86), 150 mg twice daily (n=85); ^{¶¶}: nintedanib dose: 150 mg twice daily.

two and a half decades are discussed, focusing on the lessons learned to improve the management of patients with IPF. Part of the content of this article was presented at the annual congress of the European Respiratory Society in September 2015.

Lessons learned from clinical trials

Clinical trials: prednisone, azathioprine and N-acetylcysteine

Lesson learned: this triple combination should not be used in patients with IPF

The first randomised double-blind trial undertaken in IPF was of prednisone plus placebo *versus* prednisone plus azathioprine. This trial suggested a potential therapeutic benefit from prednisone plus azathioprine on lung function and survival [13]. In a separate pilot study, the addition of N-acetylcysteine (NAC), a precursor of the antioxidant glutathione, to prednisone and azathioprine improved pulmonary function tests in patients with “fibrosing alveolitis” (a term used in the 1980s–1990s likely to refer to what we currently recognise as idiopathic interstitial pneumonia) [35]. Triple therapy with prednisone, azathioprine and NAC became widely used as a treatment for IPF based on its potential to counteract the oxidative stress thought to contribute to progression of the disease. In the IFIGENIA trial, 155 randomised patients received high-dose NAC (600 mg, three times a day) or placebo, with patients in both groups receiving prednisone and azathioprine [14]. The results were promising, as patients in the triple-therapy group showed a reduced deterioration in vital capacity (VC) and diffusing capacity of the lung for carbon monoxide (DLCO) over 1 year. However, interpretation of the results was limited by the high patient drop-out rate (approximately 30% in each treatment group) and the lack of a true placebo arm.

To establish the efficacy and safety of triple therapy (NAC, prednisone and azathioprine) and NAC monotherapy, the randomised placebo-controlled PANTHER-IPF trial was conducted in 236 patients with IPF [15]. The primary endpoint was changed from baseline in FVC at week 60 but the triple-therapy arm was stopped after 32 weeks when an interim analysis showed significantly higher rates of death and hospitalisation in patients treated with triple therapy compared to placebo. The NAC monotherapy and placebo arms continued and, at the end of the trial, the results showed no overall difference between the NAC monotherapy and placebo groups in terms of change from baseline in FVC or any differences in mortality [16]. These findings resulted in a strong recommendation against the use of this triple-therapy regimen and a conditional recommendation against the use of NAC monotherapy in the most recent clinical practice guidelines for the treatment of IPF [36]. However, in a subgroup analysis, NAC was associated with a significant reduction in the risk of a composite endpoint when assessing disease progression in patients with a TT-genotype of the host defence gene *TOLLIP* but a trend towards increased risk in patients with a CC-genotype [37]. While acknowledging that these promising data come from a subgroup of patients, genotype-stratified prospective, randomised trials are required to investigate further the effects of NAC in patients with IPF [38].

Clinical trials: interferon gamma and anticoagulants

Lesson learned: the need for large placebo-controlled trials with meaningful endpoints

In 1999, results from the first trial of the cytokine interferon gamma-1b in patients with IPF showed that, after 12 months’ open-label treatment, all nine patients treated with interferon gamma-1b plus prednisolone had a substantial improvement in total lung capacity, whereas all nine patients treated with prednisolone alone showed deterioration [39]. Interest in this therapeutic approach led to a placebo-controlled trial of interferon gamma-1b in 330 patients with IPF [17]. This showed no benefit of interferon gamma-1b for progression-free survival, lung function or quality of life (table 1). The following INSPIRE trial, which assessed the effect on survival of interferon gamma-1b *versus* a placebo in 826 patients with IPF, was terminated early when an interim analysis showed no difference between treatment groups [18]. These findings were reflected in the 2011 clinical practice guidelines, which gave a strong recommendation against the use of interferon gamma in patients with IPF [1].

Pre-clinical evidence supporting a role for the coagulation cascade in fibrotic lung diseases led to the hypothesis that anticoagulation therapy might be of benefit in the treatment of IPF [40, 41]. An open-label randomised trial in 56 Japanese patients with IPF who had been admitted to hospital showed that patients treated with prednisolone and an anticoagulant had improved survival rates compared with patients treated with prednisolone alone [42]. However, due to the small size of this study and the absence of an anticoagulant monotherapy or placebo arm, considerable debate remained regarding the risk–benefit ratio of anticoagulation therapy in IPF. The randomised placebo-controlled ACE-IPF trial evaluated the efficacy and safety of warfarin in 145 patients with IPF [19]. This trial was designed to last for 48 weeks but was stopped after a mean follow-up of 28 weeks when an interim analysis showed higher mortality and a low likelihood of benefit with warfarin *versus* placebo (table 1). This led to a strong recommendation against the use of anticoagulants for the treatment of IPF in the most recent clinical practice guidelines [36]. In addition, a recent *post hoc* analysis of pooled data from 624 patients with IPF who received a placebo in

three clinical trials showed significantly higher mortality at 1 year in patients receiving oral anticoagulants for non-IPF indications, suggesting that the use of anticoagulants in patients with IPF should be based on a careful risk–benefit assessment for the individual patient, coupled with close monitoring during treatment [43].

Clinical trials: endothelin receptor antagonists

Lesson learned: effective in pulmonary arterial hypertension but not in idiopathic pulmonary fibrosis

Endothelin-1 is a mediator of epithelial–mesenchymal transition, a fundamental process in the pathogenesis of IPF [44]. The dual endothelin receptor antagonist bosentan, an approved treatment for pulmonary arterial hypertension (PAH), was investigated as a treatment for IPF in two randomised, placebo-controlled, 60-week trials: BUILD-1 and BUILD-3 [20, 21]. In the BUILD-1 trial there was no difference between bosentan and a placebo with respect to the primary endpoint (change from baseline distance in a 6-min walk distance (6-MWD) test at week 60). However, there was a numerical difference in favour of bosentan on time to disease progression or death. The BUILD-3 trial, conducted in patients with an IPF diagnosis of fewer than 3 years' duration (as confirmed by surgical lung biopsy), was designed to evaluate the effect of bosentan in a subpopulation of patients considered more likely to benefit based on the results of BUILD-1. Although bosentan was well tolerated, the BUILD-3 trial showed no difference between bosentan and a placebo with respect to the primary endpoint (worsening of IPF or death) (table 1) [21]. Similarly, although the dual endothelin receptor antagonist macitentan was generally well tolerated, the randomised placebo-controlled MUSIC trial showed no benefit with respect to the primary endpoint (change in FVC over 52 weeks) (table 1) [22]. Thus, the latest clinical practice guidelines for the treatment of IPF include conditional recommendations against the use of bosentan and macitentan [36].

Post hoc subgroup analyses of data from BUILD-1 suggested that patients with little or no honeycombing on high-resolution computed tomography (HRCT) images may have an increased response to bosentan. Based on this observation, the randomised placebo-controlled ARTEMIS-IPF trial was conducted to investigate the efficacy and safety of ambrisentan, a selective endothelin receptor antagonist approved for the treatment of PAH, in patients with IPF and minimal honeycombing. ARTEMIS-IPF was terminated after approximately 34 weeks' exposure when an interim analysis showed that there was a low likelihood of demonstrating efficacy with respect to the primary endpoint (time to disease progression) [23]. Indeed, at the time of the interim analysis a greater proportion of patients treated with ambrisentan rather than a placebo had experienced disease progression, respiratory hospitalisation and death (table 1) [23]. A strong recommendation against the use of ambrisentan was provided in the latest clinical practice guidelines for the treatment of IPF [36].

Clinical trials: etanercept

Lesson learned: not effective in idiopathic pulmonary fibrosis

Tumour necrosis factor- α (TNF- α) is a cytokine that is released by activated alveolar epithelial cells in response to injury and mediates the activation, migration and apoptosis of fibroblasts and myofibroblasts [12]. Etanercept is a recombinant human TNF receptor [45]. Between 2003 and 2005, a randomised, placebo-controlled, 48-week trial was conducted to investigate the efficacy and safety of etanercept in 88 patients with “clinically progressive” IPF [24]. This was the first prospective trial in patients with IPF to include a true placebo group and no differences in lung function endpoints were observed between treatment groups (table 1). This led to a strong recommendation against the use of etanercept in the clinical practice guidelines for the treatment of IPF published in 2011 [1]. No further trials investigating etanercept in patients with IPF have been conducted since this time.

Clinical trials: sildenafil

Lesson learned: a trial may fail to meet its primary endpoint but secondary endpoints may indicated patient benefits

Sildenafil is a phosphodiesterase-5 inhibitor that results in pulmonary vasodilation and improvements in gas exchange in patients with IPF [46]. The randomised, placebo-controlled STEP-IPF trial investigated whether sildenafil improved exercise tolerance, dyspnoea and quality of life in 180 patients with IPF and advanced lung function impairment ($DLCO < 35\%$ of predicted) [25]. There was no significant difference between the sildenafil and placebo groups with respect to the primary endpoint (proportion of patients with an improvement in 6-MWD of $\geq 20\%$ at week 12). However, there were significant benefits from sildenafil on the secondary endpoints (arterial oxygenation, $DLCO$, dyspnoea and health-related quality of life assessed using the St George's Respiratory Questionnaire (SGRQ)). In a subgroup analysis of patients with right-ventricular systolic dysfunction, those treated with sildenafil had a significantly lower decline in 6-MWD and greater improvement in health-related quality of life than patients treated with a placebo [47].

A conditional recommendation against the use of sildenafil was given in the latest clinical practice guidelines for the treatment of IPF (table 2) [36]; however, sildenafil continues to be investigated as a potential therapy in patients with IPF and severe lung function impairment, for example, in the ongoing randomised INSTAGE trial of sildenafil given in combination with nintedanib *versus* nintedanib alone (<https://clinicaltrials.gov/ct2/show/NCT02802345>) and in a randomised study of sildenafil *versus* placebo added to pirfenidone in patients with advanced IPF and intermediate or high probability of Group 3 pulmonary hypertension (<https://clinicaltrials.gov/ct2/show/NCT02951429>).

Clinical trials: imatinib

Lesson learned: not effective in idiopathic pulmonary fibrosis

Imatinib is an intracellular inhibitor of multiple tyrosine kinases implicated in fibrogenic pathways in IPF [48–50]. The efficacy and safety of imatinib were investigated in a randomised, placebo-controlled, 96-week trial in patients with IPF and the results showed no benefits for imatinib with respect to the primary endpoint (time to disease progression) (table 1) [26]. The latest clinical practice guidelines include a strong recommendation against the use of imatinib in the treatment of IPF [36].

Clinical trials: simtuzumab

Lesson learned: not effective in idiopathic pulmonary fibrosis

Simtuzumab is a monoclonal antibody against lysyl oxidase-like 2 (LOXL2), an enzyme secreted by fibroblasts that catalyses cross-linking of extracellular matrix components [51]. A Phase-II, randomised placebo-controlled trial investigating the efficacy and safety of simtuzumab in 544 patients with IPF was terminated prematurely when a preliminary analysis indicated a lack of efficacy on the primary endpoint (progression-free survival) [27]. No further trials investigating agents that act against LOXL2 in patients with IPF have been initiated.

Clinical trials: pirfenidone

Lesson learned: reduces disease progression in patients with idiopathic pulmonary fibrosis with a manageable safety and tolerability profile

The pyridone derivative pirfenidone exhibits a number of antifibrotic, anti-inflammatory and anti-oxidant effects *in vitro* and in animal models of lung fibrosis [52–54]; however, it is unclear which of these effects occurs at the doses achieved in humans. Initial observations from a single-arm Phase-II trial suggested potential benefits from pirfenidone in stabilising FVC, total lung capacity and DLCO in patients with IPF [55]; however, a randomised, placebo-controlled, Phase-II trial conducted with 107 Japanese IPF patients was terminated prematurely after an interim analysis at 6 months showed a higher frequency of acute exacerbations in the placebo group [28]. At the time of the interim analysis there was no significant benefit from pirfenidone on the primary endpoint (change in oxygen saturation during a 6-min steady state exercise test); however, decline in VC was significantly reduced in the pirfenidone group. Three randomised, placebo-controlled, Phase-III trials were initiated to investigate the effect of pirfenidone on lung function: one in Japan and two in North America and Europe (the CAPACITY trials). In the

TABLE 2 Current recommendations for the pharmacological treatment of idiopathic pulmonary fibrosis (IPF) [36]

Agent	Guidance [#]	Strength of guidance
Warfarin	Strong recommendation against use	Moderate confidence in effect estimates
NAC, prednisone and azathioprine	Strong recommendation against use	Low confidence in effect estimates
NAC monotherapy	Conditional recommendation against use	Low confidence in effect estimates
Bosentan	Conditional recommendation against use	Low confidence in effect estimates
Macitentan	Conditional recommendation against use	Low confidence in effect estimates
Ambrisentan	Strong recommendation against use	Low confidence in effect estimates
Sildenafil	Conditional recommendation against use	Moderate confidence in effect estimates
Imatinib	Strong recommendation against use	Moderate confidence in effect estimates
Anti-acid therapy [¶]	Conditional recommendation for use	Very low confidence in effect estimates
Nintedanib	Conditional recommendation for use	Moderate confidence in effect estimates
Pirfenidone	Conditional recommendation for use	Moderate confidence in effect estimates

NAC: N-acetylcysteine; [#]: Strong recommendation: most patients would want the suggested course of action. Conditional recommendation: the majority of patients would want the suggested course of action. Different choices will be appropriate for different patients depending on individual values and preferences. [¶]: Although anti-acid therapy received a conditional recommendation for use in this guideline, this was not based on evidence from prospective randomised controlled trials. No such trials have been conducted and are needed to determine the risk-benefit ratio in patients with IPF without symptomatic gastroesophageal reflux.

Japanese trial, pirfenidone significantly reduced decline in VC at week 52 [29]; however, results from the two CAPACITY trials were conflicting. The primary endpoint (change from baseline FVC (% predicted) at week 72) was met in CAPACITY 2 but not in CAPACITY 1 [30]. The reason for these discordant efficacy results was unknown and the US Food and Drug Administration requested an additional randomised, placebo-controlled trial to confirm the effectiveness of pirfenidone in patients with IPF. In the ASCEND trial, treatment with pirfenidone for 52 weeks significantly reduced decline in FVC (% predicted) compared with a placebo (table 1) and had a safety and tolerability profile consistent with previous trials (characterised predominantly by gastrointestinal adverse events and rash) [31]. Subgroup analyses of pooled data from the CAPACITY and ASCEND trials indicated a consistent effect for pirfenidone across patient subgroups defined by a number of baseline characteristics [56]. Results from a pooled analysis of data from the Japanese, CAPACITY and ASCEND trials demonstrated a reduction in all-cause mortality with pirfenidone *versus* a placebo (relative risk: 0.70; 95% CI: 0.47–1.02) [36]. Pirfenidone has been approved as a treatment for IPF in several countries and regions and received a conditional recommendation in the most recent clinical practice guidelines (table 2) [36].

Clinical trials: nintedanib

Lesson learned: reduces disease progression in patients with idiopathic pulmonary fibrosis with a manageable safety and tolerability profile

Nintedanib is an intracellular inhibitor of tyrosine kinases involved in the pathogenesis of IPF, including vascular endothelial growth factor receptor, fibroblast growth factor receptor and platelet-derived growth factor receptor [57–59]. It has demonstrated antifibrotic and anti-inflammatory effects in *in vitro* experiments and in animal models [58–60]. The efficacy and safety of nintedanib in patients with IPF were investigated in the Phase-II randomised, placebo-controlled, dose-finding TOMORROW trial. This trial showed that nintedanib (150 mg twice daily over 52 weeks) was associated with a reduced annual decline in FVC, fewer acute exacerbations and preservation of health-related quality of life (as measured using the SGRQ) *versus* a placebo [32]. In the two replicate, randomised, placebo-controlled, Phase-III INPULSIS trials, nintedanib (150 mg twice daily) significantly reduced the annual rate of decline in FVC *versus* a placebo. Furthermore, significant benefits were observed for nintedanib *versus* a placebo with respect to key secondary endpoints (time to first-investigator-reported acute exacerbation and change from baseline in SGRQ total score) in INPULSIS-2 but not in INPULSIS-1 [33]. The most frequent adverse event was diarrhoea, which was manageable for most patients. Subgroup analyses of pooled data from the INPULSIS trials showed that nintedanib had consistent effects across subgroups of patients defined by a variety of baseline characteristics, including lung function and diagnostic criteria (including honeycombing on HRCT and/or confirmation of usual interstitial pneumonia (UIP) by biopsy *versus* possible UIP and traction bronchiectasis on HRCT and no surgical lung biopsy) [61–63]. In a pooled analysis of data from the TOMORROW and INPULSIS trials, nintedanib reduced the risk of all-cause mortality compared with a placebo (relative risk: 0.70; 95% CI: 0.47–1.03) [36]. Nintedanib has been approved as a treatment for IPF in several countries and regions and received a conditional recommendation in the most recent clinical practice guidelines (table 2) [36].

Lessons learned on the natural history of idiopathic pulmonary fibrosis

Observations from the placebo groups of clinical trials have provided valuable insights into the clinical course of IPF. Across clinical trials, the decline in FVC in placebo-treated patients with IPF and mild or moderate impairment in lung function at baseline was approximately 150–200 mL·year⁻¹ (figure 2). However, the clinical course of IPF was highly variable, with some patients deteriorating rapidly while in others FVC remained stable for the duration of the trial. Data from large clinical trials have confirmed that prediction models based on commonly measured clinical variables are generally poor predictors of disease progression [66]. In an analysis of pooled data from placebo-treated patients in the CAPACITY and ASCEND trials, change in FVC was highly variable and could not be predicted based on change in the previous 6 months [67]. Interestingly, in the INPULSIS trials, placebo-treated patients with FVC >90% of predicted at baseline experienced a very similar decline in FVC over 52 weeks as those with baseline FVC ≤90% of predicted [62], suggesting that patients with preserved FVC should not be regarded as being at low risk of disease progression.

Acute exacerbations of IPF (identified using different methodologies) were reported in 2–16% of placebo-treated patients over 24–60 weeks, while mortality ranged from 2.5–13.3% over approximately 28–96 weeks [16, 18–26, 30–33]. Data from the INPULSIS trials suggests that events adjudicated as confirmed or suspected acute exacerbations were associated with similar post-event mortality as other forms of acute respiratory worsening [68]. This supports the perspective of an international working group that the requirement for an event to be idiopathic should be removed from the definition of an acute exacerbation [5].

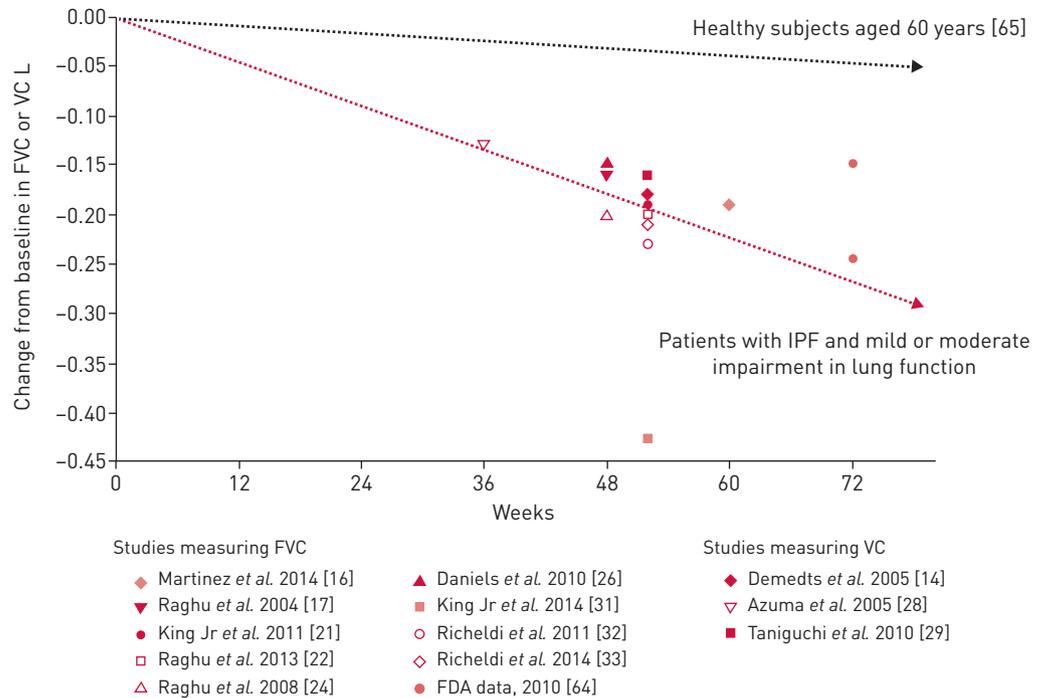


FIGURE 2 Natural course of lung function decline in placebo-treated patients with idiopathic pulmonary fibrosis (IPF) from the time of enrolment in clinical trials to 72 weeks. The decline in forced vital capacity (FVC) from baseline is approximately 150–200 mL·year⁻¹ (0.15–0.2 L·year⁻¹). The symbols denote the mean (or median [21, 22]) change from baseline in FVC [16, 17, 21, 22, 24, 26, 31–33, 64] or vital capacity (VC) [14, 28, 29] in the placebo groups of Phase-II and Phase-III clinical trials in patients with IPF. The black line denotes the mean decline in FVC in healthy subjects aged 60 years based on FVC measurements taken between 1987–1989, 1990–1992 and 2011–2013 [65].

Patients with IPF frequently experience comorbidities that may impact the course of the disease, including PAH, lung cancer, chronic obstructive pulmonary disease and gastroesophageal reflux disease [69, 70]. Effective identification and treatment of comorbidities are an important part of the care of patients with IPF.

Conclusions

Over the past two and a half decades remarkable accomplishments have been achieved in the clinical management of IPF. Our understanding of the pathogenesis of disease has greatly improved and has influenced the choice of compounds investigated as potential therapies. Despite being an orphan disease, several large, multicentre, randomised clinical trials have been conducted, culminating in the approval of two drugs for the treatment of IPF. Scientific theory has been confirmed or debunked with evidence, improving the standard of care for patients with IPF and sparing patients from receiving ineffective and, in some cases, potentially harmful drugs. We have learned that what is biologically plausible and effective in non-clinical studies does not always translate to improved outcomes in the clinic. We have also learned valuable lessons on how to conduct pragmatic clinical trials in IPF. Progress in the management of IPF would not have been possible were it not for investigators, clinicians, patients, patient advocacy groups, donors and sponsors including the pharmaceutical industry working together towards a common goal. Future trials will investigate novel therapeutics, combination and sequential treatment, measures that better assess outcomes that are meaningful to patients (including effects on symptoms and quality of life), the use of antifibrotic therapies in patients with common comorbidities, and the use of predictive and prognostic biomarkers to enable more precision medicine. Timely and accurate diagnosis of IPF will remain critical in ensuring that patients can receive appropriate care and support from an early stage of disease.

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