

The treatment of idiopathic pulmonary fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive and invariably fatal disease with a median survival of less than three years from diagnosis. The last decade has seen an exponential increase in clinical trial activity in IPF and this in turn has led to important developments in the treatment of this terrible disease. Previous therapeutic approaches based around regimens including corticosteroids and azathioprine have, when tested in randomized clinical trials, been shown to be harmful in IPF. By contrast, compounds with anti-fibrotic actions have been shown to be beneficial. Subsequently, the novel anti-fibrotic agent pirfenidone has, in many parts of the world, become the first treatment ever to be licensed for use in IPF. This exciting development, coupled with ongoing clinical trials of a range of other novel compounds, is bringing hope to patients and their clinicians and raises the prospect that, in the future, it may become possible to successfully arrest the development of progressive scarring in IPF.

Introduction

IPF is a disease characterized by progressive scarring of the lung and carries an appalling prognosis [1]. The etiology of IPF remains unknown, thus the development of successful treatments has lagged behind other fields in medicine. Nevertheless, with the combination of increased understanding of IPF disease pathogenesis and intensified efforts from the pharmaceutical industry, all this is beginning to change. This short commentary will, in light of recent clinical trial developments, provide an overview of the changing landscape of IPF treatments.

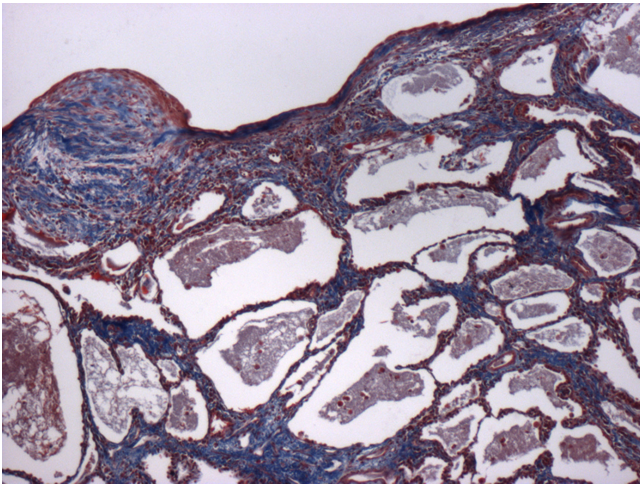
Idiopathic pulmonary fibrosis

IPF is a disease that occurs more commonly in men and typically occurs in individuals aged between 40 and 70 years. The incidence of IPF is 6.8 to 16.3 per 100,000 and this figure is on the increase [2,3]. In the UK, IPF accounts for 5000 deaths per year, a figure far in excess of many cancers, including myeloma, lymphoma, and stomach cancer [3]. Individuals with IPF present with progressive breathlessness and cough, which, although usually mild at the outset, inevitably becomes disabling

with time. Almost all those with IPF eventually die from respiratory failure, with median survival from diagnosis being less than 3 years. The 5-year survival for IPF, which stands at 20%, is worse than that of adenocarcinoma of the lung.

The pathogenesis of IPF remains incompletely understood. It was previously considered that inflammation preceded fibrosis, but the lack of efficacy and, moreover, deleterious effects of immunosuppressive therapy have led to a shift in thinking. Available evidence points to IPF developing in genetically susceptible individuals as a consequence of an aberrant wound-healing response arising following repetitive alveolar injury [1,4]. It appears that alveolar epithelial injury drives fibroblast proliferation, myofibroblast differentiation, and collagen deposition, leading to the formation of fibrotic foci, the hallmark histological feature of IPF. This laying down of collagen and extracellular matrix stiffens the lungs and destroys the delicate lace-like structure of the alveolar spaces (Figure 1). Ultimately, gas exchange is impaired, leading to respiratory failure and death.

Figure 1. Low-power photomicrograph illustrating the characteristic appearances of usual interstitial pneumonia, the histological lesion of idiopathic pulmonary fibrosis (IPF)



The image shows fibroblastic foci overlying a region of micro-cystic honeycomb change. The sections have been stained with a Trichrome stain. This clearly highlights the extensive collagen (stained blue) and extracellular matrix deposition that occurs in IPF.

None of the compounds currently under evaluation in clinical trials are able to reverse the scarring which characterizes IPF. This has necessitated a paradigm shift when it comes to evaluating treatment success in IPF. The goal of treatment, in this otherwise devastating and fatal disease, is not to improve lung function but instead simply to prevent progression of disease (and thus preserve functional status and quality of life). Stability in lung function, which has hitherto frequently been considered a failure of treatment by physicians and patients, should be regarded as a successful outcome.

This article will summarize the IPF trials that have influenced treatment together with the key negative trials that have informed current clinical trial activity. Promising compounds now in early-phase trials will be very briefly reviewed.

Trials that have shaped the idiopathic pulmonary fibrosis treatment landscape

The first true randomized placebo-controlled trial (RCT) in IPF was published as recently as 2004 [5]. This trial of the TH₁ cytokine interferon- γ 1b, although ultimately negative, proved an important watershed for the field of interstitial lung disease. For the first time, it was demonstrated that it is possible to recruit and follow up for 12 months sufficient numbers of patients with IPF to make appropriately powered RCTs a feasible prospect. It should

be noted that an important foundation stone to this study was the development and publication of the first international guidelines and consensus statement on the diagnosis of IPF [6]. Without internationally accepted diagnostic criteria (and separation of IPF from other forms of idiopathic interstitial pneumonitis), it would not have been possible for multi-center international studies to develop. Since the publication of these consensus guidelines and the interferon- γ study, there has been an exponential growth in clinical trial activity in IPF [7]. Whilst many of these trials have ultimately proved negative (as detailed in Table 1), each individual study has provided important insights in to optimal trial design and choice of end-points. Furthermore, as will be described, these studies have culminated in the licensing, in Europe, Japan, India, and Canada, of the first specific treatment for IPF, pirfenidone [8].

N-acetyl-cysteine

The IFIGENIA (Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual) study, a multi-center, RCT of high-dose oral N-acetylcysteine (NAC) compared with placebo, published in 2005 [9], was the first RCT in IPF to achieve its primary end-point. In this trial, NAC was given in addition to what, at the time, was the recommended standard therapy for IPF: a tapering dose of oral prednisolone combined with the immunosuppressant azathioprine.

NAC is a precursor of glutathione, a free radical scavenger and an important endogenous antioxidant in the lung [10]. Oxidative stress-mediated injury of alveolar epithelial cells is important in the pathogenesis of IPF [11]. However, glutathione levels are markedly reduced in the lungs of individuals with IPF [12]. Small pilot studies in IPF demonstrated that orally administered NAC results in increased lung glutathione levels [13,14]. This observation paved the way for the IFIGENIA trial.

In the IFIGENIA study, when compared with placebo, treatment with 1800 mg/day NAC led to a significant reduction in absolute forced vital capacity (FVC) decline (9% $P < 0.02$) and diffusion capacity (DL_{CO}) decline (24% $P < 0.003$) [9]. There was no difference in the number of deaths between arms at one year; however, the study was not powered for survival. NAC was safe and well tolerated. Although positive, the study has attracted some criticism; firstly, the numbers of subjects completing treatment at 12 months were relatively small. Secondly, all patients were on immunosuppression and so the true effect of NAC alone is unknown; and, thirdly, the findings have yet to be replicated. Despite this and

Table 1. A summary overview of negative randomized placebo-controlled trials undertaken in idiopathic pulmonary fibrosis

Compound	Study	Study design	Patients	Primary end-point	Results
Warfarin (anticoagulant)	ACE-IPF [45] 2012	Phase III Warfarin vs. placebo for 48 weeks	n = 256 terminated at 145	Composite of all-cause mortality, hospitalization and $\geq 10\%$ absolute FVC decline	Increased mortality in warfarin arm (14 vs. 3 deaths in placebo arm $P = 0.005$). Study terminated at unscheduled interim analysis by the DSMB.
Everolimus (mTOR inhibitor)	Malouf et al. [46] 2011	Phase II 4 mg bd Everolimus vs. placebo for 3 years	n = 89	Time to disease progression defined by the time to the second of any two of a 10% change in FVC or TLC; 15% change in DL _{CO} ; a 4% point change in resting room air SaO ₂	Increased disease progression in everolimus arm (180 days vs. 450 days in placebo arm $P < 0.01$). Higher frequency of AEs in patients in everolimus arm.
Bosentan (dual endothelin receptor antagonist)	BUILD1 [47] 2008	Phase III Bosentan 125 mg bd vs. placebo for 1 year	n = 158	BUILD1: change in 6MWT at 12 months	No significant change in 6MWT between treatment groups but post hoc analysis showed a trend towards reduced mortality in patients in the bosentan arm who had undergone a surgical lung biopsy.
	BUILD3 [48] 2011	Phase III Bosentan 125 mg bd vs. placebo for 3 years	n = 616	BUILD3: time to disease progression ($\geq 10\%$ absolute FVC decline or $\geq 15\%$ decline in DL _{CO} or acute exacerbation)	No significant difference in time to disease progression in patients diagnosed with a surgical lung biopsy.
Ambrisentan (type A endothelin receptor antagonist)	ARTEMIS [49] IPF 2013	Phase III Ambrisentan 10 mg vs. placebo for 18 months.	n = 660 terminated at 492	Time to disease progression defined by death or respiratory hospitalization, $\geq 10\%$ absolute FVC decline or $\geq 15\%$ decline in DL _{CO} or acute exacerbation	Terminated at interim analysis due to lack of efficacy. Increased disease progression in ambrisentan arm (n = 90 (27.4%) vs. n = 28 (17.2%) in placebo arm $P = 0.01$). Increased respiratory hospitalizations in ambrisentan arm (n = 44 (13.4%) vs. n = 9 (5.5%) in placebo arm $P = 0.007$).
Macitentan (dual endothelin receptor antagonist)	MUSIC trial [50] 2013	Phase II Macitentan 10 mg vs. placebo for 1 year	n = 178	Change in FVC at 12 months	No significant difference in change in absolute FVC between treatment groups.
Sildenafil (phosphodiesterase-5 inhibitor)	STEP-IPF [51] 2010	Phase III Sildenafil 20 mg tds vs. placebo for 12 weeks, followed by 12-week open-label extension with all patients receiving sildenafil	n = 180	$\geq 20\%$ increase in the 6MWT at 12 weeks	No significant difference in the number of patients with $\geq 20\%$ increase in 6MWT distance, but significant improvement in secondary outcomes DL _{CO} and QOL scores.
Interferon γ-1b (Th1 cytokine)	Raghu et al. [5] 2004	Phase III 200 μ g subcutaneous IFN γ -1b vs. placebo 3 times weekly for 48 weeks	n = 330	Progression-free survival	No significant difference in progression-free survival.
	INSPIRE [52] 2009	Phase III 200 μ g subcutaneous IFN γ -1b vs. placebo 3 times weekly for 96 weeks	n = 826	Overall survival time from randomization	No significant survival benefit with IFN γ -1b at second interim analysis hence study terminated at this point.
Etanercept (recombinant soluble human TNF-α receptor)	Raghu et al. [53] 2008	Phase II Etanercept 25 mg vs. placebo twice weekly for 48 weeks	n = 88	Changes from baseline in FVC% predicted, DL _{CO} % predicted and P(a-a)O ₂ at rest.	No significant difference in primary end-points between etanercept and placebo groups.

(Continued)

Table 1. A summary overview of negative randomized placebo-controlled trials undertaken in idiopathic pulmonary fibrosis (Continued)

Compound	Study	Study design	Patients	Primary end-point	Results
Imatinib (tyrosine kinase inhibitor with activity against PDGF receptors, c-kit and c-abl) Co-trimoxazole (antibiotic)	Daniels et al. [54] 2010	Phase II Imatinib 600 mg vs. placebo for 96 weeks	n = 119	Time to disease progression (10% decline in percent predicted FVC from baseline) or time to death.	No significant difference in survival or lung function between treatment groups.
	Shulgina et al. [55] 2013	Phase II Co-trimoxazole 960 mg twice daily vs. placebo for 52 weeks	n = 181	12 month change in FVC	No significant difference between groups in FVC but improved survival in treatment adherent subjects

6MWT, 6-minute walk distance; AE, adverse effect; ARTEMIS, Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF; bd, *bis in die* (twice daily); BUILD, Bosentan Use in Interstitial Lung Disease; DL_{CO}, carbon monoxide diffusing capacity; DSMB, Data and Safety Monitoring Board; FVC, forced vital capacity; IFN, interferon; INSPIRE, interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis; IPF, idiopathic pulmonary fibrosis; mTOR, mammalian target of rapamycin; MUSIC, Macitentan for the treatment of idiopathic pulmonary fibrosis; PDGF, platelet-derived growth factor; QOL, quality of life; SaO₂, oxygen saturation; STEP-IPF, Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis; TLC, total lung capacity; TNF, tumor necrosis factor.

because of its good safety profile, NAC is widely used as a treatment for IPF.

To address the issues raised by the IFIGENIA study, the National Institutes of Health-funded United States IPF network designed the PANTHER-IPF study (Prednisolone, Azathioprine and N-acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis) [15]. PANTHER-IPF is a 60-week, double-blind, RCT with three treatment arms: (i) combination (triple) therapy of azathioprine, prednisolone, and NAC; (ii) NAC monotherapy; and (iii) placebo. At interim safety analysis, triple therapy was associated with an increase in all-cause mortality (8 patients in the combination arm vs. 1 in placebo arm), an increase in the rate of hospitalization (29% vs. 8%), and an excess of serious adverse events (31% vs. 9%) [15]. Furthermore, triple therapy failed to show any treatment benefit (measured using FVC) when compared with placebo. In light of these results, the independent Data and Safety Monitoring Board terminated treatment in the triple-therapy arm. The NAC monotherapy and placebo arms of the study were continued, and the last visit of the last patient has now occurred. Results are anticipated in early 2014. In the meantime, the results from the triple-therapy arm of the PANTHER-IPF study have had significant repercussions and led to a rapid shift away from the use of immunosuppressants as a treatment for IPF.

Pirfenidone

Pirfenidone, a pleotropic, orally available, small molecule with anti-fibrotic, anti-oxidant, and anti-inflammatory effects [8], has become the first drug to be licensed specifically for the treatment of IPF. Pirfenidone reduces growth factor-driven fibroblast proliferation and extracellular matrix production *in vitro* and attenuates

experimentally induced pulmonary fibrosis *in vivo* in animal models [16,17].

Following several small open-label studies [18-20], the first RCT of pirfenidone for IPF was completed in Japan in 2005. The study by Azuma et al. was terminated early because of an excess of acute exacerbations in the placebo arm (a finding not repeated in any subsequent study) [21]. The study did not achieve its primary end-point of change in lowest arterial oxygen saturation during a 6-minute walk. There was, however, a significant reduction in FVC decline at 9 months in the treatment arm ($P = 0.0366$). Subsequent to this study, there have been three completed phase III RCTs of pirfenidone compared with placebo in IPF. Two of these studies have met their primary end-point of reduction in FVC decline.

The first phase III trial was a Japanese multi-center double-blind placebo-controlled trial conducted over 52 weeks [22]. Patients were randomized to high-dose (1800 mg/day) pirfenidone, low-dose (1200 mg/day) pirfenidone, or placebo. A significant improvement in FVC decline (-0.09 L vs. -0.16 L $P < 0.0416$) and progression-free survival was seen in the high-dose treatment arm compared with placebo. The CAPACITY (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) 1 and 2 phase III multinational randomized double-blind placebo trials ran concurrently [23]. CAPACITY 1 ($n = 435$) assessed the efficacy of high-dose (2403 mg/day) pirfenidone, low-dose pirfenidone (1197 mg/day), and placebo. CAPACITY 2 ($n = 344$) had only two treatment arms; high-dose pirfenidone (2403 mg/day) and placebo. The end-point for both trials was change in FVC at week 72. In CAPACITY 1, the high-dose treatment arm met the

primary end-point with a significant reduction in decline in FVC at week 72 compared with placebo (-8% vs. -12.4% $P = 0.001$). Unfortunately, CAPACITY 2 failed to meet its primary end-point, although improvements were seen in some secondary end-points. Notably, no effect on quality-of-life scores was observed in any of these trials. Whilst generally safe, pirfenidone does cause a number of side effects, including gastrointestinal upset and photosensitivity rash, which impact its tolerability.

A recent Cochrane meta-analysis of the four published pirfenidone trials demonstrated that treatment with pirfenidone reduced the risk of disease progression by 30% (hazard ratio 0.70, 95% confidence interval 0.56 to 0.88) [24]. On the basis of these studies, the European Medicines Agency approved the use of pirfenidone in 2011. Pirfenidone is also licensed in Japan, India, and Canada. In contrast, the US Food and Drug Administration, having discounted the results of the two Japanese studies, refused approval of pirfenidone based on the failure of the CAPACITY 2 trial to meet its primary end-point. Consequently, a further US-based phase III RCT, the ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in IPF) trial (NCT01366209), commenced in 2011. The primary end-point for the study is change in percent predicted FVC over a 52-week period. Results are expected in early 2014.

Nintedanib

There has been an exponential increase in the number of compounds entering clinical trials for IPF in the last decade [25]. Of the drugs currently in development, the closest to clinic is the novel tyrosine kinase inhibitor nintedanib (Boehringer Ingelheim, Ingelheim am Rhein, Germany) (formerly known by its development name BIBF 1120) [26]. Originally developed as an angiogenesis inhibitor for use in oncology indications, nintedanib proved to have anti-fibrotic activity *in vitro* in human lung fibroblasts and *in vivo* in the rodent model of bleomycin-induced pulmonary fibrosis [27]. In the phase II, double-blinded RCT TOMORROW (To improve pulMONary fibROsis With BIBF1120) study, 432 patients with IPF were treated with placebo or one of four escalating doses of nintedanib for 52 weeks [28]. The primary end-point of change in FVC was narrowly missed when the highest-dose (150 mg twice daily) treatment arm was compared with placebo ($P = 0.06$). Treatment with nintedanib was associated with fewer acute exacerbations and improved quality-of-life scores. The results of the TOMORROW study were sufficiently compelling for two parallel phase III studies (NCT01335464 and NCT01335477) of nintedanib in IPF to be undertaken. These two trials have recently been completed, and results are anticipated in early 2014.

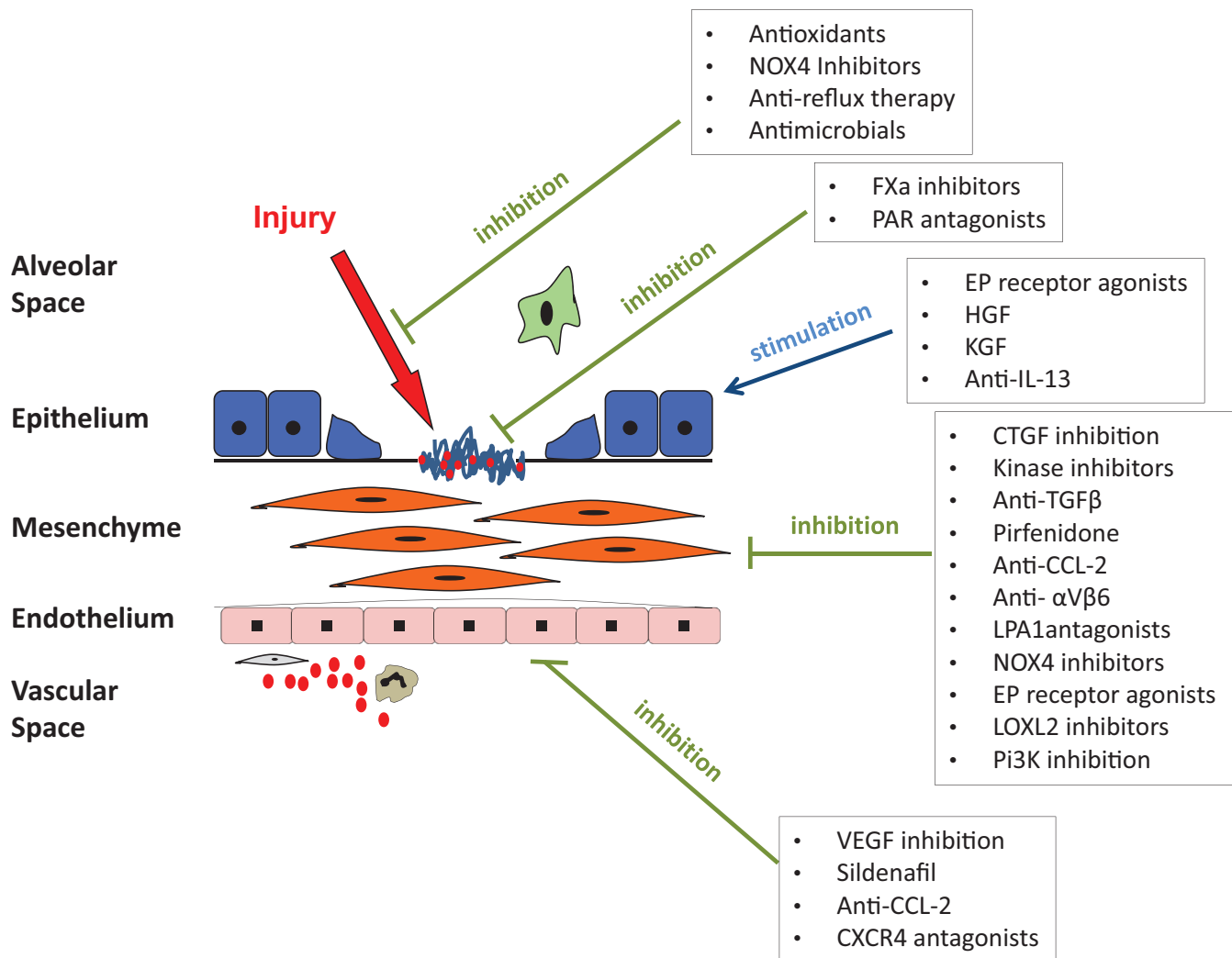
Potential future idiopathic pulmonary fibrosis treatments

As understanding of the pathogenesis of IPF has improved, the number of potential therapeutic targets has increased dramatically. Strategies that have been considered include (a) prevention of alveolar epithelial injury, (b) targeting the coagulation cascade, (c) stimulating epithelial proliferation, inhibiting epithelial apoptosis, and increasing epithelial resistance to injury, (d) inhibition of fibroblast proliferation and collagen synthesis, (e) direct targeting of the extracellular matrix, (f) inhibition of transforming growth factor-beta (TGF- β) and other pro-fibrotic cytokines, and (g) targeting the capillary endothelium, principally to prevent the development of pulmonary hypertension. These potential approaches and compounds in development are outlined in Figure 2 [29].

A multitude of novel compounds are currently in various stages of clinical trial development. It is beyond the scope of this article to consider all but the most developed of these potential therapies. For a more detailed review of compounds in development, please refer to [29]. The three drugs in most advanced development are covered briefly below.

- a) Simtuzumab (Gilead Sciences, Foster City, CA, USA – formerly known as AB0024) is a humanized monoclonal antibody against lysyl oxidase-like 2 (LOXL2) [30-32]. The lysyl oxidases are a group of enzymes that catalyze the cross-linking of type 1 collagen molecules. LOXL2 expression is increased in IPF and promotes collagen accumulation and deposition [31]. In the murine bleomycin model, simtuzumab effectively attenuates the development of fibrosis [30]. Simtuzumab is now being tested in a large multi-center phase IIb RCT in IPF (NCT0176196).
- b) Lebrikizumab (Roche, Basel, Switzerland) is a humanized monoclonal antibody against interleukin (IL)-13. In the lungs of patients with IPF, IL-13 is found at increased concentrations [33]. *In vitro* IL-13 stimulates fibroblast proliferation, whilst *in vivo*, IL-13 overexpression results in increased fibrosis in mice in response to bleomycin [34]. Lebrikizumab has been shown to have efficacy in severe asthma [35] and is now being tested in IPF in a large phase IIb study (NCT01872689).
- c) STX-100 (Biogen Idec, Weston, MA, USA) is a humanized monoclonal antibody targeted against the integrin $\alpha v \beta 6$. TGF- β is a critical pro-fibrotic growth factor that is believed to play a critical role in the development of fibrosis [36]. The $\alpha v \beta 6$ integrin functions as an activator of TGF- β . In mice, inhibition of $\alpha v \beta 6$ attenuates the development of bleomycin-induced fibrosis [37].

Figure 2. A schematic outlining potential new idiopathic pulmonary fibrosis (IPF) therapies as they relate to the proposed pathogenetic events involved in the development of idiopathic pulmonary fibrosis



Modified from [29] with permission.

Consequently, STX-100 is being tested in a phase 2 study in IPF (NCT01371035).

Challenges and controversies

After decades of stagnation, it is very exciting to see the great strides that are being taken in the search for treatments for IPF. Whilst current developments are a cause for great optimism, there are a number of important areas within the field of IPF clinical trials that require addressing.

a) In the last year or two, there has been considerable controversy around the choice of optimal end-point for IPF studies. It has been suggested that survival should be used as the primary end-point in registration studies as it is both clinically meaningful and

robust [38]. While this might be the case, important practical considerations such as the number of subjects needed to power a survival study and the ethical difficulty of asking study subjects to continue in a study through to death when they may be receiving placebo treatment alone means that annual change in FVC currently remains the end-point of choice [39-42]. Better quantification of the relationship between FVC change and both mortality and quality of life is necessary so that clinical trial outcomes can be better understood [43].

b) In recent times, all phase 2b and phase 3 studies have excluded the use of other “anti-fibrotic” therapies. Whilst this was feasible in an era where there were no

licensed treatments for IPF, it is an approach that is becoming harder to justify. The situation at the moment is complicated by the fact that pirfenidone is not yet licensed in all territories; however, this is likely to change if the ASCEND study is positive. Whilst on the face of it permitting the use of other therapies in clinical trials should not create major issues, it will narrow the therapeutic window in which efficacy of a new compound can be measured and it also raises the prospect of interactions and altered tolerability.

- c) To date, the majority of new compounds trialed for IPF have gone straight in to late-phase studies with very few having been rigorously tested in early-phase studies. The principal reason for this has been the lack of robust short-term end-points demonstrating inhibition of fibrotic pathways. The lack of an agreed-upon proof-of-concept study design is a barrier to entry in to the IPF arena for many smaller pharmaceutical companies. It is important that the IPF field focus on developing robust, validated surrogate end-points, which will enable the easier translational development of compounds from the laboratory through to the clinic [44].

Conclusions

IPF is a devastating disease with a poorer prognosis than many cancers. In recent times, a multitude of different cellular pathways have been identified as potential therapeutic targets. Accompanying this, there has been a huge increase in the number of compounds entering clinical trials. Although the majority of trials have yielded negative results, a great deal has been learnt about the natural history of IPF and its pathogenesis. The lack of efficacy and detrimental effects of immunosuppression has led to a paradigm shift with IPF no longer being thought of as an inflammatory disease. Consequently, pharmacotherapy has evolved to focus on anti-fibrotic strategies. To date, pirfenidone is the only treatment to show a significant effect in slowing the inevitable declining lung function that characterizes IPF. It is to be hoped, however, that compounds currently in clinical trials will lead to further transformation of the clinical landscape in IPF. In turn, these ongoing developments should be a source of hope to individuals with IPF and to their treating physicians.

Abbreviations

ASCEND, (Assessment of Pirfenidone to Confirm Efficacy and Safety in IPF); CAPACITY, Clinical Studies Assessing Pirfenidone in Idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes; FVC, forced vital capacity; IFIGENIA, Idiopathic Pulmonary Fibrosis

International Group Exploring N-Acetylcysteine I Annual); IL, interleukin; IPF, idiopathic pulmonary fibrosis; LOXL2, lysyl oxidase-like 2; NAC, N-acetylcysteine; PANTHER-IPF, Prednisolone, Azathioprine and N-acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis; RCT, randomized placebo-controlled trial; TGF- β , transforming growth factor-beta; TOMORROW, To improve pulMONaRy fibROsis With BIBF1120.

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