

PHARMACOLOGICAL TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS - AN UPDATE

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common and most lethal fibrosing interstitial pneumonia, with a mortality rate that exceeds that of many cancers. Currently, there is no standard treatment recommended by the guidelines. A number of high-quality clinical trials evaluating novel potential therapies have recently been concluded. While the results have mostly been disappointing, some compounds appear promising in reducing disease progression. In this regard, pirfenidone is the most advanced molecule for IPF treatment, having been approved in Europe, Japan, India, and Canada. However, due to the complexity and uncertainties intrinsic to IPF, it is essential that each therapeutic strategy be tailored to the individual patient, after evaluation of potential benefits and pitfalls. Randomised controlled trials represent a valid choice for IPF patients. Many agents with high potential are being tested and many more are ready to be tested in clinical trials. Their completion is critically important to achieve the ultimate goal of curing IPF.

Keywords: Idiopathic pulmonary fibrosis, clinical trials, pirfenidone, treatment.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial pneumonia of unknown cause, limited to the lung and associated with the histopathological (evidence of patchy involvement of lung parenchyma by fibrosis/architectural distortion, honeycombing in a predominantly subpleural/paraseptal distribution, presence of fibroblastic foci; **Figure 1**) and/or radiological (subpleural, basal-predominant honeycombing and reticular abnormality, with or without traction bronchiectasis; **Figure 2**) pattern of usual interstitial pneumonia (UIP).¹ The diagnosis of IPF is established in the presence of a UIP pattern on high-resolution computed tomography (HRCT) of the chest and/or surgical lung biopsy (SLB) specimen, in the appropriate

clinical setting (commonly a current or ex-smoker male of >60 years of age) and after the exclusion of all known causes of pulmonary fibrosis.¹ The disease, which primarily affects older adults, carries a dismal prognosis with a median survival time in retrospective longitudinal studies of 2 to 3 years after diagnosis,²⁻⁵ although recent data from placebo arms of large clinical trials, which recruited patients with mild to moderate disease, have reported a longer survival.¹

In the last decade, the pharmacological treatment of IPF has changed considerably, mirroring the evolving understanding in disease pathogenesis. Initially, the prevailing hypothesis was that a persistent inflammation eventually triggered scarring of the lung. As such, early studies evaluated the potential efficacy of drugs that primarily

suppress inflammatory or immune responses, such as corticosteroids and immunomodulatory agents; the results of these trials have all been uniformly disappointing. Over the last decade the perspective on IPF pathogenesis has profoundly changed, and current concepts suggest that there is an initial alveolar epithelial cell damage followed by an aberrant healing response resulting in the migration, proliferation and activation of mesenchymal cells, accompanied by focal accumulation of myofibroblasts, known as fibroblast foci. Progressive laying down of extracellular matrix proteins and destruction of lung architecture complete the histopathological picture.⁶ Accordingly, more recent randomised controlled trials have shifted their focus to molecules with anti-fibrotic and anti-proliferative

properties. However, the pathogenesis of IPF remains incompletely understood and the rationale for evaluating the efficacy of specific compounds has often derived from post-hoc analyses of previous studies. Drugs approved for the treatment of other diseases, but with some evidence of potential efficacy in fibrotic disorders, have also been evaluated in IPF clinical trials.

Available therapeutic options for IPF have recently been systematically assessed according to the GRADE methodology (Table 1).¹ Thus, for the very first time, clinicians confronted with a patient with IPF can base their clinical decisions on the evidence derived from data of randomised-controlled trials.

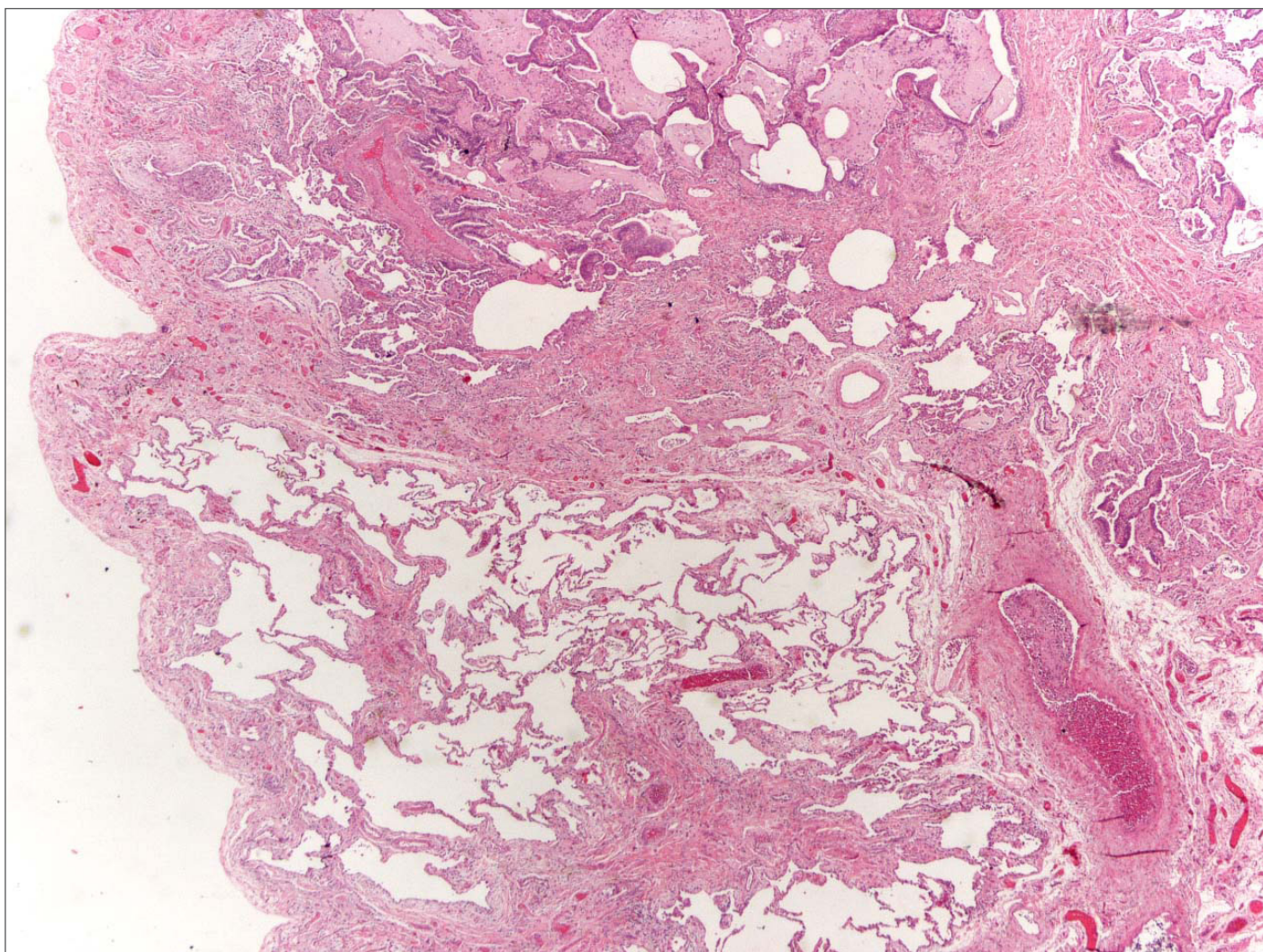


Figure 1. Surgical lung biopsy showing usual interstitial pneumonia (UIP) pattern, characterised by the abrupt juxtaposition of scarred lung with honeycombing (top) and nearly normal lung (bottom). Several pale fibroblastic foci are also seen.

Haematoxylin-eosin, 20x. Courtesy Alberto Cavazza, Reggio Emilia, Italy.

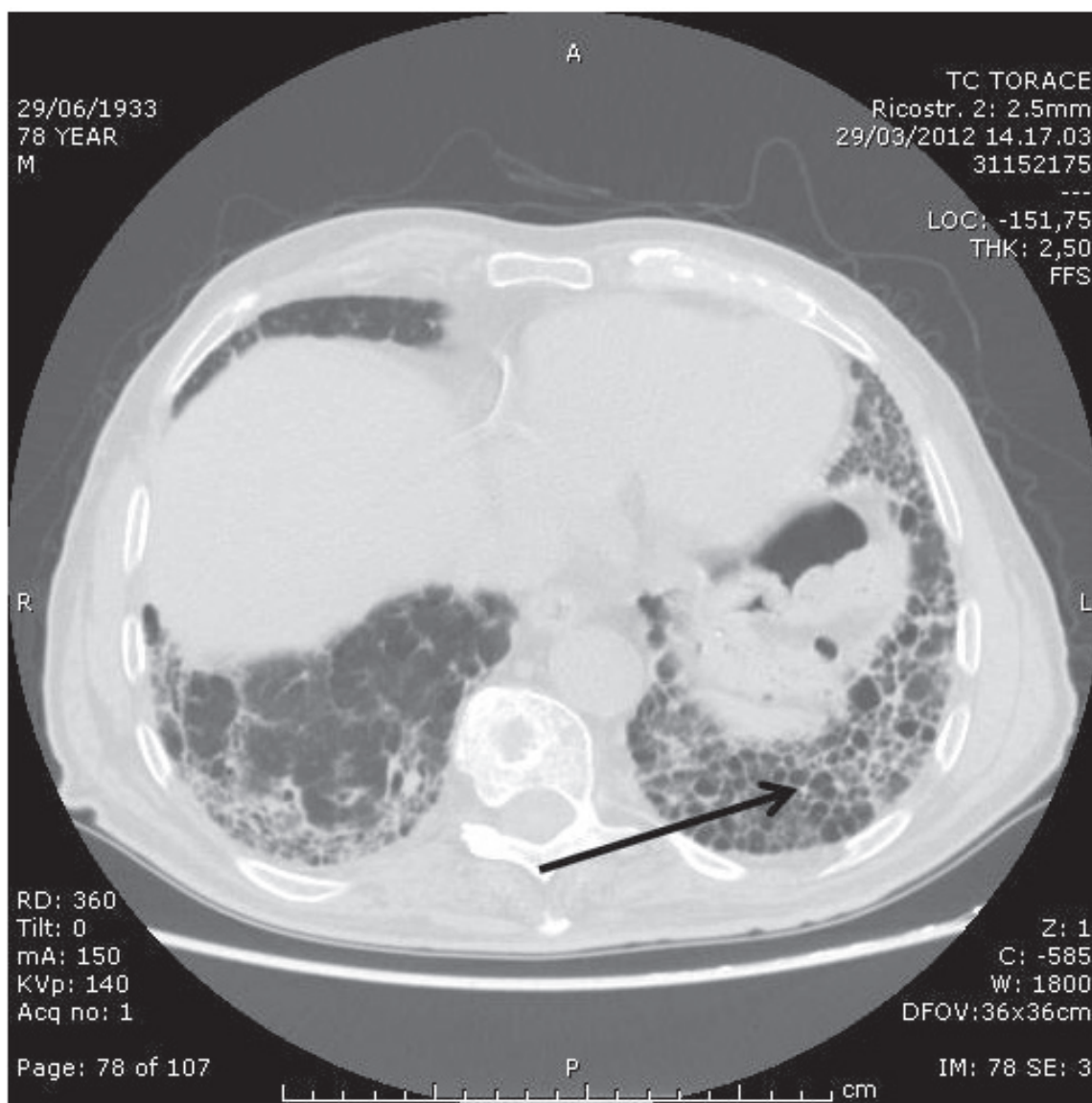


Figure 2. High-resolution computed tomography (HRCT) image of usual interstitial pneumonia (UIP) pattern showing basal and peripheral predominant reticular abnormality with subpleural honeycombing (more extensive at the left lung base; arrow).

ANTI-INFLAMMATORY AND IMMUNOMODULATORY DRUGS

Early studies in IPF largely focused on the effects of corticosteroids because of their anti-inflammatory effects and wide use in clinical practice in any fibrotic lung disorder. However, these studies were mostly conducted prior to the international guidelines published in 2000 and likely included patients with idiopathic interstitial pneumonias other than IPF, such as nonspecific interstitial pneumonia (NSIP), which would be more responsive to anti-inflammatory therapies.⁷ Yet, two recent systematic reviews did not identify any high-quality

trial evaluating the efficacy of corticosteroids in IPF.^{8,9} On the other hand, long-term corticosteroid treatment is associated with significant morbidity and potentially severe side-effects. Accordingly, current evidence-based guidelines make a strong recommendation against the use of corticosteroid monotherapy in IPF, despite the absence of any randomised placebo-controlled trial.¹ Similarly, limited and low-quality evidence of efficacy is available for non-steroid immunomodulatory drugs, such as colchicine, cyclosporin A, cyclophosphamide or azathioprine, either alone or in combination with corticosteroids,¹⁰ and current guidelines place a strong recommendation against their use in IPF.¹

Azathioprine, an antimetabolite, blocks most T cell functions, inhibits primary antibody synthesis, and decreases the number of circulating monocytes and granulocytes.¹¹ In a prospective, double-blind, placebo-controlled trial, 27 patients were randomised in a 1:1 ratio to prednisone (1.5 mg/kg/day for 2 weeks, with a bi-weekly taper until a maintenance dose of 20 mg/day) plus either placebo or azathioprine (3 mg/kg/day to a maximum of 200 mg/day).¹² After 1 year, changes

in lung function, as measured by resting P[A-a]O₂, forced vital capacity (FVC), and diffusing capacity of the lung for carbon monoxide (DLCO), were all slightly better in the azathioprine/prednisone group than in the prednisone/placebo group, although none of these comparisons were statistically significant. Yet, azathioprine in combination with low dose corticosteroids has long represented the standard of care in IPF.⁷

Table 1. Summary of the current evidence-based recommendations on pharmacological treatment of patients with IPF.

Strength	Recommendation							
	For				Against			
	Weak		Strong		Weak		Strong	
Quality of evidence	L/VL	M/H	L/VL	M/H	L/VL	M/H	L/VL	M/H
Corticosteroids alone							X	
Colchicine							X	
Cyclosporin A							X	
Cyclophosphamide + corticosteroids							X	
Azathioprine + corticosteroids							X	
Azathioprine + corticosteroids + NAC*					X			
NAC alone					X			
Interferon-γ-1b								X
Bosentan								X
Etanercept								X
Anticoagulants*					X			
Pirfenidone					X			
Long-term oxygen			X					
Lung transplant			X					
Mechanical ventilation					X			
Pulmonary rehabilitation	X							
Treatment of pulmonary hypertension					X			
Steroids in acute exacerbation of IPF	X							
Asymptomatic gastro-oesophageal reflux	X							

(Modified from Raghu G. et al.)

L: low; VL: very low; M: medium; H: high

NAC: N-acetylcysteine.

*Recommendations on these drugs are likely to change in the near future based on the results from recently published clinical trials.

Note: official recommendations are not available for sildenafil and imatinib, as the results of clinical trials evaluating these drugs have been published after the publication of the ATS/ERS/JRS/ALAT 2011 guideline document.¹ See text for details.

ANTIOXIDANTS

The IFIGENIA (Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine), a double-blind, randomised, placebo-controlled multicentre study, assessed the efficacy over 1 year of a high oral dose (600 mg three times daily) of N-acetylcysteine (NAC), a precursor of the antioxidant glutathione (GSH) synthesis that has been shown to be reduced in the lungs of patients with IPF,¹³ added to standard therapy, i.e. a combination of prednisone and azathioprine.¹⁴ NAC had previously been shown to increase the GSH levels in the bronchoalveolar lavage fluid (BALF) and improve lung function in patients with fibrosing alveolitis.¹⁵ In comparison to prednisone plus azathioprine (the 'placebo' arm), the so-called triple therapy significantly slowed the decline of both vital capacity (VC) and DLCO (the primary endpoints). Specifically, at 12 months, the absolute differences in the change from baseline between patients taking NAC and those taking placebo were 0.18 litres or a relative difference of 9%, for VC ($p=0.02$), and 0.75 mmol per minute per kilopascal or 24%, for DLCO ($p=0.003$).

Weaknesses of this study related mainly to the lack of a true placebo arm (i.e. patients not taking any potentially effective drug), the lack of a survival benefit, the high rate (about 30%) of patients lost to follow-up at 12 months due to death or withdrawal and the consequent statistics utilised, and the least squared last observation carried forward for imputations approach, which tends to preserve the sample size from high drop-out rate but may make unwarranted assumptions about the missing data, potentially resulting in either underestimation or overestimation of the treatment effects. Due to these drawbacks, and in spite of the positive results of the study, recent guidelines make a weak recommendation against the use of this combination therapy, i.e. the majority of patients with IPF should not be treated with the triple therapy, although this may represent a reasonable therapeutic option in a minority of patients.¹

The National Heart, Lung and Blood Institute (NHLBI)-sponsored IPFnet consortium designed a placebo-controlled, randomised three-arm trial, the PANTHER-IPF (Prednisone, Azathioprine, and N-acetylcysteine: A Study That Evaluates Response in IPF), to confirm the efficacy of N-acetylcysteine in IPF.¹⁶ In this study patients were randomly assigned in a 1:1:1 ratio to prednisone, azathioprine and NAC (combination therapy), NAC alone, or placebo. The primary outcome was the change in longitudinal

FVC measurements over a 60 week period. Secondary outcomes included mortality, time to death, frequency of acute exacerbations, and time to disease progression as defined by a composite endpoint of death or relative drop in FVC $\geq 10\%$. Unexpectedly, a pre-specified efficacy and safety interim analysis, planned at approximately 50% of data collection, showed that the combination therapy, as compared to placebo, was associated with a statistically significant increase in all-cause mortality (11% versus 1%), all-cause hospitalisations (29% versus 8%), and treatment-related severe adverse events (31% versus 9%). These observations, coupled with the lack of evidence of physiological or clinical benefit for the combination therapy, prompted the data and safety monitoring board to recommend termination of the combination therapy group at a mean follow-up of 32 weeks, while the NAC alone and the placebo arms continue to enroll patients. These largely unexpected results not only provide evidence against the use of this combination of drugs in patients with IPF but also underscore the importance of placebo-controlled trials in areas where the effects of treatment are largely based on limited evidence or low-quality data.

INTERFERON-GAMMA-1B

Interferon gamma-1b (IFN- γ -1b), a protein with antifibrotic and immunomodulatory properties, is secreted primarily by T cells (CD4 T cells, CD8 T cells, and natural killer cells). A pilot study by Ziesche and co-workers¹⁷ showed that the association of IFN- γ -1b and prednisolone (as compared with prednisolone alone) improved lung function and partial pressure of arterial oxygen at rest in patients with IPF. However, in a subsequent large randomised, double-blind, placebo-controlled phase III trial, in which IPF patients were randomly assigned to receive subcutaneous IFN- γ -1b 200 μ g three times weekly ($n=162$) or placebo ($n=168$), the primary endpoint of progression-free survival, defined by time to disease progression or death, was not achieved.¹⁸ Similarly, no significant treatment effect was observed on lung function, gas exchange, extent of fibrosis on HRCT, or quality of life. However, post-hoc analyses suggested that patients with mild-to-moderate impairment in lung function at study entry might be more likely to benefit from IFN- γ -1b treatment. Moreover, a reduced mortality (10%) was observed in the IFN- γ -1b arm as compared with the placebo arm (17%), although this difference was not statistically significant. A subsequent meta-analysis, involving

390 patients, confirmed that treatment with IFN- γ -1b significantly reduced mortality in patients with IPF.¹⁹ Based on these findings, a larger randomised-controlled trial of over 800 patients (International study of Survival outcomes in idiopathic Pulmonary fibrosis with InteRfEron gamma-1b: the INSPIRE trial) was specifically designed to assess the efficacy of IFN- γ -1b on survival time in IPF patients with mild-to-moderate impairment in baseline pulmonary function.²⁰

However, a protocol-defined interim analysis revealed that the hazard ratio for mortality among patients treated with IFN- γ -1b crossed the predefined stopping boundary for lack of minimal benefit. After a median treatment duration of 77 weeks, 14.5% of patients in the IFN- γ -1b group had died compared to 12.7% of patients in the placebo group ($p=0.497$). As such, the guidelines make a strong recommendation against the use of IFN- γ -1b in patients with IPF.¹

DRUGS ACTING ON THE PULMONARY VASCULATURE

Data from basic science, animal, and translational studies suggest that the endothelin system, and endothelin (ET)-1 in particular, is a potential contributor to the pathobiology of several fibrotic disorders, including IPF.²¹ In fact, ET-1 has been shown to modulate matrix production and turnover, leading to increased collagen synthesis and decreased interstitial collagenase production.²²

Bosentan

In a double-blind, placebo-controlled study (Bosentan Use in Interstitial Lung Disease: BUILD-1), 158 IPF patients were randomly assigned to receive either bosentan, a dual ET_A receptor antagonist (ET_A and ET_B), or placebo.²³ Bosentan did not meet its primary endpoint (change in 6 minute walk test distance [6MWD] by month 12). However, a post-hoc analysis revealed a trend in favour of bosentan in time to death or disease progression in patients with limited honeycombing on HRCT whose diagnosis had been obtained by surgical lung biopsy. This finding formed the basis for a second, prospective, randomised (2:1), double-blind, placebo-controlled trial (BUILD-3) that enrolled patients with IPF ($n=616$) of less than 3 years' duration, diagnosed histologically, and with <5% of honeycombing on HRCT.²⁴ Unfortunately, the primary endpoint (death or disease progression defined by a decline $\geq 10\%$ in FVC and $\geq 15\%$ in

DLCO or an acute exacerbation of IPF at month 12) was not met. Bosentan was well-tolerated, but its lack of efficacy makes it a non-viable treatment option for IPF.¹

Ambrisentan

Ambrisentan is a selective antagonist of the ET_A receptor, approved for the treatment of pulmonary arterial hypertension.²⁵ Endothelin-1 induces lung fibroblast proliferation and contractile activity via the ET_A receptor.²⁶ Importantly, preclinical studies have shown that both the phenotypic and transcriptional responses to ambrisentan are different from bosentan, suggesting that clinical effects in IPF may also be different.²⁷ The ARTEMIS-IPF (Randomised, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF) was a randomised, double-blind, placebo-controlled, multi-national trial, evaluating effectiveness of ambrisentan in reducing disease progression (defined as death, respiratory hospitalisation or decline in lung function). The study was terminated earlier, after enrolment of 492 patients (75% of intended enrolment), following an interim analysis indicating a low likelihood of efficacy for the primary endpoint.²⁸ Indeed, ambrisentan was associated with an increased risk of disease progression and respiratory hospitalisations.

Macitentan

Macitentan, a dual endothelin receptor antagonist, has been shown to prevent the development of lung fibrosis in a mouse model.²⁹ The MUSIC (Macitentan Use in Idiopathic pulmonary fibrosis Clinical) trial, a prospective, randomised, double-blind, multicentre, parallel-group, placebo-controlled, phase II proof-of-concept study evaluated the efficacy and safety of macitentan in IPF patients.³⁰ Of the 178 randomised patients, 119 were allocated to macitentan and 59 to placebo. The study did not meet its primary endpoint (change from baseline up to month 12 in FVC). Similarly, no differences were observed between treatment groups in any of the secondary or exploratory measures including time to IPF worsening or death.

Sildenafil

Sildenafil, a phosphodiesterase-5 inhibitor that induces pulmonary vasodilatation by stabilising the second messenger of nitric oxide (cyclic guanosine monophosphate), is approved for the treatment

of pulmonary arterial hypertension.^{31,32} In a small open-label study, the oral administration of sildenafil at the dose of 25-50 mg three times daily improved the 6MWD by a mean of 49 metres.³³ These observations prompted a large phase III double-blind, placebo-controlled study (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis: STEP-IPF) in which 180 subjects were randomised to sildenafil (20 mg three times daily) or placebo for 12 weeks, with a subsequent 12-week open label phase in which all patients received the active drug.³⁴ The difference in the primary outcome was not significant, with 9 of 89 patients (10%) in the sildenafil group and 6 of 91 (7%) in the placebo group having an improvement of ≥ 20 meters in the 6MWD ($p=0.39$). However, significant differences favouring sildenafil were observed in the change in PaO₂, DLCO, degree of dyspnoea, and quality of life. The presence of some positive secondary outcomes creates clinical equipoise for further research. At present, there is no evidence to support the routine use of sildenafil in IPF.

Etanercept

Etanercept is a recombinant soluble monoclonal antibody that binds and neutralises tumour necrosis factor (TNF)- α receptor. The rationale for its use in IPF comes from the observations that TNF- α has inflammatory and fibrogenic properties, and elevated levels of this cytokine have been detected in the lungs of patients with IPF.^{35,36} In addition, in mouse models, TNF- α antagonists diminish bleomycin-induced pulmonary inflammation and fibrosis,³⁷ suggesting a potential beneficial effect in patients with IPF. A randomised, prospective, double-blind, placebo-controlled, multicentre phase II trial evaluated the safety and efficacy of subcutaneous etanercept (25 mg twice weekly).³⁸ After 48 weeks of treatment, no significant differences in any of the efficacy endpoints (changes in the percentage of predicted FVC or DLCO, and in the P(A-a)O₂ at rest from baseline) were observed between the groups. As such, the use of etanercept in IPF is not recommended.¹

Pirfenidone

Pirfenidone, an orally administered pyridine with antifibrotic, anti-inflammatory and antioxidant properties,³⁹ is the only drug approved for clinical use in the treatment of IPF.⁴⁰ In an open-label study, 54 IPF patients were treated with pirfenidone and followed for mortality, change in lung function, and

adverse effects.⁴¹ Pirfenidone appeared to slow the decline in lung function and enabled corticosteroid dosage to be reduced to discontinuation in the majority of patients. In a subsequent larger multicentre, randomised, double-blind, placebo-controlled phase II trial, 107 Japanese patients were assigned to receive either an escalating dosage of pirfenidone or placebo.⁴² The primary endpoint (change in the lowest blood oxygen saturation (spO₂) during a 6 minute exercise test) was not met. However, positive treatment effects were observed in change in VC at 9 months and rate of acute exacerbations, which occurred exclusively in the placebo group, although this latter effect has not been replicated in subsequent studies. Pirfenidone was associated with significant adverse events - with skin photosensitivity, gastro-intestinal symptoms, and liver function test abnormalities being the most common - although there was no significant difference in the treatment discontinuation rate between the two groups at 9 months.

In a subsequent larger multicentre, double-blind, placebo-controlled phase III study, 275 Japanese patients with IPF were randomly assigned in a 2:1:2 ratio to high-dose (1,800 mg/day) or low-dose (1,200 mg/day) pirfenidone, or placebo over a 52 week period.⁴³ The study met its primary endpoint, change in VC. In fact, the rate of decline of VC was higher in the placebo arm (-0.16 L) compared to both the high-dose (-0.09 L; $p=0.042$) and low-dose pirfenidone arms (0.08 L; $p=0.039$). Significant differences were also observed in progression-free survival time between the high-dose and the placebo arms ($p=0.028$) and in the changes in total lung capacity (TLC) between the low-dose and the placebo arms ($p=0.040$). A limitation of this study is the change of the primary endpoint before unblinding, which could possibly have hampered the integrity of the study. An exploratory analysis of this same study revealed that patients with a baseline VC $\geq 70\%$ and oxygen saturation $< 90\%$ had a greater benefit from pirfenidone.⁴⁴ Similar to the previous study, photosensitivity was the most common drug-related adverse event (observed in 51% of patients in the high-dose group and 53% in the low-dose group), but not a major reason for discontinuation of the study.

The CAPACITY studies (CAPACITY 1 - PIPF 006 and CAPACITY 2 - PIPF 004) are two almost identical randomised, double-blind, placebo-controlled, multinational phase III clinical trials that evaluated

the efficacy of oral pirfenidone over 72 weeks.⁴⁵ In the 004 trial, patients were assigned in a 2:1:2 dosing ratio to pirfenidone 2,403 mg/day, pirfenidone 1,197 mg/day, or placebo, while in study 006, patients were assigned in a 1:1 ratio to pirfenidone 2,403 mg/day or placebo. The primary endpoint was change in percentage predicted FVC at week 72. In study 004, mean FVC change at week 72 was -8.0% in the pirfenidone 2,403 mg/day group and -12.4% in the placebo group ($p=0.001$). Conversely, in the 006 study, the change in FVC at week 72 was not significant between the treatment and placebo arms ($p=0.501$). Of note, while the magnitude of decline over time was similar in the two active arms, in the two placebo groups it differed. Specifically, in the study PIPF 006 the placebo arm displayed an attenuated FVC decline (-9.6%) as compared to the placebo arms of other large clinical trials of IPF.⁴⁶

All these trials had sufficient methodological quality to be included in a Cochrane systematic review and meta-analysis, which confirmed that pirfenidone reduces both the rate of decline of lung function and the risk of disease progression (as measured by progression-free survival) as compared to placebo.¹⁰ Some limitations to the interpretation of these data still apply, mainly related to a certain degree of methodological heterogeneity across studies with regard to reporting of lung function data.

Pirfenidone has been granted marketing authorisation for the management of patients with mild to moderate IPF in Japan in 2008, and in Europe in 2011. Despite this, the use of pirfenidone has not been approved by the Food and Drug Administration (FDA) due to a perceived lack of efficacy as measured by change in FVC, and lack of survival benefit.⁴⁷ A new phase III trial of pirfenidone aiming to confirm the positive effect on FVC is therefore underway in the US (the ASCEND trial, clinicaltrials.gov; identifier NCT01366209). Current guidelines, considering the cost of pirfenidone and the potentially relevant side-effects make a weak recommendation against its use in IPF. Regardless, patients willing to receive pirfenidone should be fully informed on the available evidence for its efficacy as well as on the possible side-effects.

ANTICOAGULANTS

Anticoagulants have been evaluated in IPF based on evidence of their efficacy in ameliorating pulmonary fibrosis in animal models when given either

prophylactically or therapeutically.^{48,49} Based on this pathogenetic hypothesis, 56 Japanese patients with IPF were randomly assigned to receive prednisolone alone or prednisolone plus anticoagulant therapy (oral warfarin, which was switched to low-molecular-weight heparin in case of hospitalisation for acute deterioration) in an open label study.⁵⁰ While the incidence of acute exacerbations (AE) did not differ between the groups, there was an increased mortality associated with AE in the non-anticoagulant group compared to the anticoagulant group (71% versus 18%, respectively; $p=0.008$). Limitations of the study included lack of blinding; patient recruitment (e.g. there may have been a selection bias toward more advanced and rapidly progressive disease); substantial withdrawal rate in the anticoagulant group (26%) (e.g. it is likely that patients who left the study were more ill and would have had higher mortality); failure to exclude pulmonary embolism as a potential cause of acute deterioration (e.g. mean plasma levels of D-dimer were significantly higher in patients who died from AE). As such, treatment with anticoagulants is not recommended for routine use in patients with IPF (weak recommendation against, very low-quality evidence).¹

To further investigate the utility of anticoagulation in IPF, the NHLBI sponsored the AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) trial.⁵¹ In this study patients were randomly assigned in a 1:1 ratio to warfarin or matching placebo for a planned treatment period of 48 weeks. Due to excess mortality in the warfarin arm (14 warfarin versus 3 placebo deaths; adjusted HR=4.85), the study was terminated after 145 of the planned 256 subjects were enrolled (72 warfarin, 73 placebo). Similar trends favouring placebo were observed in all-cause hospitalisations, respiratory-related hospitalisations, and AE of IPF. In partial accordance with the current guideline recommendations, the results of this study strongly argue against the routine use of warfarin for the treatment of IPF. As such, recommendations on this drug are very likely to change in the near future.

TYROSINE KINASE INHIBITORS

Tyrosine kinases regulate a variety of physiological cell processes, including metabolism, growth, differentiation and apoptosis, and aberrant tyrosine kinase activity has been shown to promote the development and progression of both neoplastic and non-neoplastic diseases.^{52,53} Signalling

pathways activated by tyrosine kinases have also been suggested to be implicated in the pathogenesis of lung fibrosis.⁵⁴

Nintedanib (BIBF 1120)

The TOMORROW (To Improve Pulmonary Fibrosis With BIBF 1120) study, a 12-month, randomised, double-blind, placebo-controlled trial, evaluated the safety and efficacy of BIBF 1120,⁵⁵ a tyrosine kinase inhibitor that suppresses pro-angiogenic intracellular signalling by targeting the proliferative growth factor receptors on platelets (PDGFR), vascular endothelium (VEGFR) and fibroblasts (FGFR).⁵⁶ Four different oral doses of BIBF 1120 (50 mg once a day, and 50 mg, 100 mg, or 150 mg all twice a day) were tested. BIBF 1120 at a dose of 150 mg twice daily showed a trend toward a reduction in the decline in FVC, the primary endpoint. Specifically, in the group receiving 150 mg of BIBF 1120 twice a day, FVC declined by 0.06 litres per year, as compared to 0.19 litres per year in the placebo group; a 68.4% reduction in the rate of loss. In addition, patients treated with 150 mg of BIBF 1120 twice daily had a lower incidence of AE and an improvement in quality of life (small decrease in St. George's Respiratory Questionnaire score as compared with an increase with placebo). Overall, BIBF 1120 showed an acceptable safety profile, although diarrhoea, nausea, vomiting, and increases in levels of liver aminotransferases - the most common drug-related side-effects - were more frequent in the group receiving 150 mg of BIBF 1120 twice daily than in the placebo group. These results warranted the investigation of BIBF 1120 in phase III clinical studies, with results expected in 2014.

Imatinib

Imatinib, a tyrosine kinase inhibitor with activity against several fibrogenic factors (including PDGFR- α and β), has been investigated in IPF based on its ability to inhibit lung fibroblast-myofibroblast transformation and proliferation as well as extracellular matrix production in animal models of pulmonary fibrosis.⁵⁷ In a phase II, randomised, double-blind, placebo-controlled study, 119 patients with mild or moderate IPF were randomly assigned to receive imatinib (600 mg orally once daily; n=59) or placebo (n=60) for 96 weeks.⁵⁸ The study found neither a survival benefit nor an effect on FVC, the primary outcome. Similarly, no differences in any of

the predefined secondary endpoints were observed between the imatinib and the placebo groups. As such, imatinib does not represent a therapeutic option for patients with IPF.

Co-trimoxazole

Following a pilot study of 20 patients with idiopathic interstitial pneumonias (IIP), in which co-trimoxazole treatment improved FVC, shuttle walk distance and Medical Research Council (MRC) dyspnoea score,⁵⁹ a larger randomised placebo-controlled double-blind parallel group clinical trial was designed to assess the efficacy and safety of the addition of 12 months of oral co-trimoxazole (960 mg twice daily) to usual treatment in fibrotic IIP (definite or probable IPF, n=170; definite or probable NSIP, n=11).⁶⁰ No significant difference was observed between treatment groups for change in FVC, the primary outcome. However, co-trimoxazole reduced mortality (a tertiary endpoint), a finding somewhat unexpected and possibly related to a reduction of respiratory infection. In fact, patients receiving immunosuppressive treatment were more likely to die if they were in the control group, whereas baseline immunosuppressive therapy did not have an effect on mortality in the intervention group. In addition, the difference between groups in survival was observed with the per-protocol analysis but not with the intention-to-treat analysis. Drawbacks of the study include the high dropout rate because of side-effects among patients receiving co-trimoxazole, the lack of a true placebo arm, the inclusion of both IPF and NSIP patients, and poorly defined diagnostic criteria.

ANTI-GASTRO-OESOPHAGEAL REFLUX DRUGS

Abnormal acid gastro-oesophageal reflux (GER) is common in patients with IPF and is considered a risk factor for the development of the disease.^{61,62} Retrospective studies have shown longer survival in patients given anti-acid treatment.⁶³ A recent study analysed the change in FVC in patients randomly assigned to the placebo arms in three large randomised controlled trials. After adjustment for gender, baseline FVC, and baseline DLCO, patients taking anti-acid treatment at baseline (proton-pump inhibitors or H₂ blockers) had a smaller decrease in FVC at 30 weeks compared to those not taking anti-acid treatment (p=0.05).⁶⁴ Anti-acid treatment could be beneficial in patients with IPF, and current guidelines recommend the treatment of asymptomatic GER

in patients with IPF (weak recommendation, very low-quality evidence). However, controlled clinical trials of anti-acid treatments are now needed.

EMERGING TREATMENTS

Treatment of IPF has always been challenging and, for more than 20 years, patients have been given treatments that were not appropriate (if not harmful). The future however looks bright owing to a continuous flow of information that provides new insights in disease pathogenesis. This has resulted in an exponentially increasing number of potential therapeutic targets, and currently there are more than 60 clinical trials in IPF that are either recruiting or about to start patient recruitment (www.clinicaltrials.gov).

Transforming Growth Factor β

Transforming growth factor β (TGF- β) is considered to play a key role in pulmonary fibrosis as it interferes with almost all the processes involved in its development, such as chemotaxis and proliferation of fibroblasts, differentiation of fibroblasts into myofibroblasts, which represent the major source of extracellular matrix, epithelial-mesenchymal transition, and inhibition of myofibroblasts apoptosis.^{65,66} At present, there are three known isoforms of the protein: TGF- β 1, 2 and 3. Multiple strategies to inhibit TGF- β activities exist. The first is to directly block TGF- β by using human monoclonal antibodies. Antibodies against TGF- β 1, 2 and 3 have been developed (GC1008 Genzyme) and a phase I trial has been completed, but the data has yet to be published. Another way is by interfering with the activation of the protein. Before the protein becomes active, cleavage of the latency associated protein is necessary, which is performed by the integrin $\alpha\beta$ 6. A potential agent directed against $\alpha\beta$ 6 has been identified in animal models (STX-100). This is an important intermediate in the activation of latent TGF- β .⁶⁷

Connective Tissue Growth Factor

Connective tissue growth factor (CTGF) is thought to be a central mediator of tissue remodelling and fibrosis.⁶⁸ Following promising results in animal models, a phase II trial evaluated safety and efficacy of anti-CTGF antibodies (FG-3019; clinicaltrials.gov identifier NCT01262001) in patients with IPF. Preliminary data showed improvement or stability of fibrosis (as determined by HRCT) after

24 weeks of treatment, with this improvement being positively associated with changes in FVC. However, full results of this study are yet to be published in a peer-reviewed publication.⁶⁹

Interleukin-13

Interleukin-13 (IL-13) is a profibrotic protein found to be increased in BALF of patients with IPF.⁷⁰ IL-13 induces TGF β , PDGF and other profibrotic agents such as insulin-like growth factor and connective tissue growth factor. A human anti-IL-13 antibody has been developed (QAX576), and is currently being tested in a phase II trial. The results are eagerly awaited.

Lysyl Oxidase-Like 2

Lysyl oxidase-like 2 (LOXL2) plays a role in cross-linking monomeric collagen fibers, that are secreted by fibroblasts. This maturation process, which makes the extracellular matrix stiffer, impacts on the progression of fibrosis.⁷¹ LOXL2 has been shown to be upregulated in patients with IPF.⁶ In the bleomycin-induced pulmonary fibrosis mouse model a monoclonal antibody against LOXL2 induced a reduction in inflammatory cytokines, and activated fibroblasts and fibrillar collagen.⁷² A study evaluating the efficacy of an anti-LOXL2 antibody has recently started patient recruitment.

Chemokine (C-C Motif) Ligand 2

An important, but for a long time neglected, cell in pulmonary fibrosis is the macrophage. When macrophages become polarised to the M2 phenotype, they may promote collagen synthesis. Chemokine (C-C motif) ligand 2 (CCL2) regulates monocyte and macrophage recruitment via the CCR2 receptor.⁷³ Recently, a study with anti-CCL2 antibody (CTNO888) has been completed and the results are expected soon.

Miscellaneous

Phosphodiesterase-4 (PDE4) is involved in cAMP metabolism, and cAMP elevation has been shown to reduce both fibroblast proliferation and matrix synthesis.⁷⁴ Roflumilast, a PDE4 inhibitor, diminishes intracellular cAMP breakdown and has been tested in other chronic lung diseases.⁷⁵ Viruses such as cytomegalovirus or Epstein-Barr virus have also been implicated in progressive pulmonary fibrosis.⁷⁶ Indeed, it has been shown that the use of intravenous ganciclovir for 2 weeks in patients with advanced IPF improved 6 minute walk test

and symptoms.⁷⁷ There are data suggesting also a potential role for antibiotics in the treatment of IPF. For instance, azithromycin has been demonstrated to slow the progression of pulmonary fibrosis in animal models. Interestingly, the effect is induced by a dose way below the antibiologically active one, thus suggesting an immunomodulatory effect.⁷⁸ Another crucial mechanism in chronic inflammatory lung disorders is the adaptive arm of the immune response, involving T_H1 and T_H2 cells, inducible regulatory T (iTreg) cells, and IL-17 producing CD4+(TH17) cells. Excessive T_H17 cell activation is observed in chronic inflammatory disorders such as psoriasis, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, and rejection after transplantation; yet, its role in interstitial lung disease remains unclear.⁷⁹

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) have the ability to home to sites of injury and contribute to epithelial restoration. As such, they have been suggested as a novel therapeutic strategy in IPF, where loss of epithelial integrity and abnormal alveolar re-epithelialisation are thought to be critical.⁸⁰ A recent phase Ib, non-randomised, clinical trial demonstrated an acceptable profile of endobronchially-administered autologous adipose-derived stromal cells.⁸¹ Carefully designed future clinical trials will clarify whether MSC could regenerate and repair diseased IPF lungs.

CONCLUSION

Over the past 10 years, substantial advances have been made in our understanding of the pathobiology of IPF. In parallel, the last decade has witnessed a steady increase in the number of high quality clinical trials being designed, undertaken and completed. This massive effort of both the medical and industry community has produced the approval for clinical use (at least in Japan, India, Europe and Canada) of the first drug for IPF: pirfenidone. In addition, the well-characterised patient populations enrolled in these studies have provided valuable insights into the natural history of the disease. Crucial information has also been gained by the lack of efficacy of specific drugs.

For instance, the failure of both anticoagulants and endothelin receptor antagonists to show any benefit in patients with IPF suggests that pathways involving the coagulation cascade or the endothelin system are not as critical, with regard to disease pathogenesis, as previously thought.

The (mostly disappointing) results of recent clinical trials in IPF highlight the challenge of identifying the 'ideal' patient population to study. Thus far, clinical studies in IPF have enrolled subjects with mild-to-moderate disease, as assessed by FVC. However, the possibility to identify individuals at highest risk of disease progression - the ones more likely to respond to any given treatment - would allow a targeted enrichment in the study population with a corresponding reduction in the required sample size.⁸² There is a continuing debate on what constitutes a clinically meaningful endpoint in clinical trials in IPF.⁸³⁻⁸⁶ While all-cause mortality is undoubtedly the most robust primary endpoint, measuring this outcome could be prohibitive because of the (large) number of patients and (long) study duration required for adequate power (particularly for patients with limited disease). As such, a number of surrogate markers for survival benefit have been proposed. Of these, change in FVC (either absolute or relative) is now the preferred primary endpoint since it closely fulfils the ideal characteristics of being reliable, reproducible, easy-to-measure, and applicable to all IPF patients,^{87,88} although not a proven surrogate of mortality.¹

A drug or drug regimen that provides a universally agreed standard of care for patients with IPF has yet to emerge. Therefore, the role of the clinician is of utmost importance in helping patients to make an informed treatment decision. Owing to the plethora of pathways potentially involved, future treatment of IPF will likely require a combination of drugs targeting diverse components of disease pathogenesis (injury, inflammation, if any, and fibrosis). Nonetheless, the current momentum in this area of research, together with experience gained and emerging insights from genetic studies, provides hope for the development of effective therapies for this devastating disease.

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