CLINICAL INVESTIGATION

Slowing progression of idiopathic pulmonary fibrosis with pirfenidone: from clinical trials to real-life experience

Idiopathic pulmonary fibrosis (IPF) is a rare, progressive, irreversible and eventually fatal fibrosing lung disease. Pirfenidone is the only approved therapy for reducing disease progression indicated in adult patients with mild to moderate IPF, which is considered the best attainable goal for a progressive and irreversible disease like IPF. Pirfenidone is an orally active, small molecule with antifibrotic and anti-inflammatory properties. Data from Phase III, randomized, double-blind, placebo-controlled trials have shown that pirfenidone reduces lung function decline and improves progression-free survival time. Pirfenidone is generally well tolerated, with the most commonly reported adverse events being gastrointestinal, dermatologic and hepatic (liver enzyme elevations) in nature. Pirfenidone was approved in Japan in 2008 and in the European Union in 2011. Since its approval in Japan, the European Union, Canada and South Korea, an increasing number of specialized centers have used it in clinical practice, confirming the tolerability profile as observed in clinical trials. With the advent of new potential drugs, combination therapy may be the way to treat patients with IPF in the future.

Keywords: antifibrotic • clinical trial • efficacy • fibroblast • idiopathic pulmonary fibrosis • pirfenidone • safety • slowing disease progression • treatment

Vincent Cottin*[1], M Wijsenbeek[2], F Bonella[3] & C Vancheri[4]

[1]Department of Respiratory Medicine, National Reference Center for Rare Pulmonary Diseases, Louis Pradel Hospital, Hospices Civils de Lyon, University Claude Bernard Lyon 1, 69677 Lyon, France

[2]Department of Pulmonary Medicine, Erasmus Medical Center, University Hospital Rotterdam, s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

[3]Department of Pulmonology & Allergology, Ruhrlandklinik, University Hospital, University of Duisburg-Essen, Tüschener Weg 40, 45239 Essen, Germany

[4]Regional Reference Center for Rare Lung Diseases, University Hospital Policlinico – Vitt. Emanuele, Via Santa Sofia 78, 95123 Catania, Italy

*Author for correspondence:
Tel.: +33 472 357 072
Fax: +33 472 357 653
vincent.cottin@chu-lyon.fr

Background

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, irreversible and eventually fatal fibrosing interstitial pneumonia limited to the lung and associated with the histological and/or radiological pattern of usual interstitial pneumonia (Figure 1) [1]. IPF is a rare disease with an estimated prevalence of 11.5/100,000 in Europe [2]. The disease typically occurs in patients over the age of 45 years; the median age at diagnosis is between 65 and 70 years of age, and it is more frequent in men than women [1,3]. The exact incidence and prevalence of IPF, which are continuously rising [4], are difficult to estimate as there may be a hidden number of asymptomatic patients with subclinical, undiagnosed disease [5,6]. IPF's prognosis is poor – with a median survival of approximately 3 years from diagnosis and a 5-year survival of approximately 20–40% [7–10], IPF is more lethal than many common malignancies [11,12].

Key clinical features of IPF include increasing breathlessness on exertion and non-productive, dry cough. Physical examination almost always reveals bibasilar inspiratory crackles on lung auscultation, which sound like Velcro® stripes being slowly torn apart, and finger clubbing [1,9,13,14]. The disease course of IPF is highly heterogeneous – some patients may experience long periods of relatively stable disease or slow progression, while others may experience rapid lung function decline and unpredictable episodes of acute exacerbations [14–16].

The etiology of IPF is unknown, but several risk factors have been associated with the disease, including cigarette smoke, exposure to environmental pollutants, metal and wood dust, viral infections and gastroesophageal reflux disease [1,15]. Genetic factors also play a

FUTURE SCIENCE part of fsg

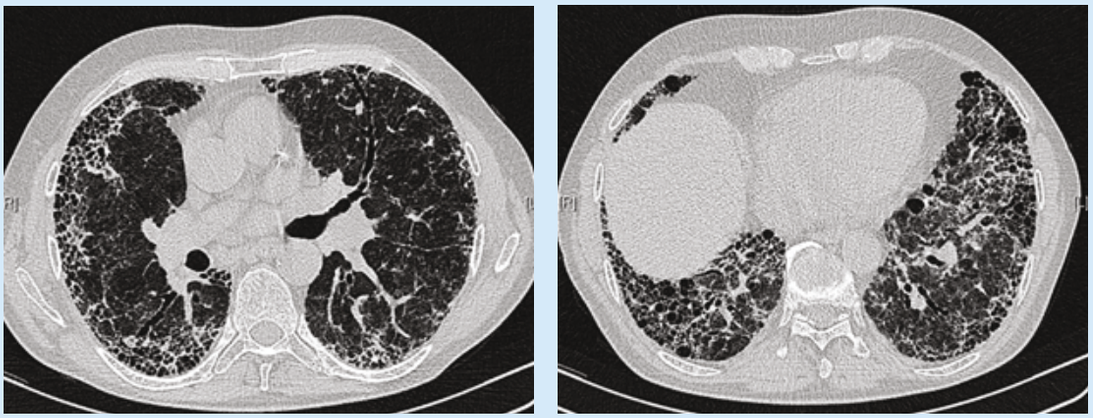

Figure 1. High-resolution computed tomography scan showing the typical pattern of usual interstitial pneumonia in a 64-year-old male patient with idiopathic pulmonary fibrosis. Main features include peripheral, predominantly basal pattern of coarse reticulation with honeycombing and the presence of traction bronchiectasis.

role in the etiology of IPF. Several gene mutations and polymorphisms increase the susceptibility to develop the disease: mutations in the *TERT* gene or the *TERC* gene are responsible for familial pulmonary fibrosis, and mutations in the *MUC5B* gene promoter, as well as polymorphism in the *SFTPA1* gene and mutations in the *SFTPA2* gene can influence the susceptibility to IPF [17–21]. According to a recent estimation, familial forms of IPF may account for up to 20% of cases [22].

The pathogenesis of IPF has not been fully elucidated. Although the disease was historically considered an inflammatory disease, the current view has shifted towards a prominent role of impaired wound healing process in response to initial injury of the alveolar epithelium. Selman *et al.* have proposed that IPF results from multiple cycles of alveolar epithelial cell injury and activation, reflecting abnormal wound repair. This in turns leads to the migration, proliferation and activation of mesenchymal cells with the formation of fibroblastic/myofibroblastic foci, and the excessive accumulation of extracellular matrix, eventually evolving to fibrosis [23,24].

It has been suggested recently that IPF and cancer share common pathways [10,11]. Similar behavioral and pathobiologic aspects include epigenetic and genetic changes, altered response to growth factors, abnormal expression of microRNAs and aberrant activation of specific signaling pathways, as well as low survival and poor response to medical treatment [11].

Diagnosis

The diagnosis of IPF requires exclusion of other known causes of interstitial lung disease (ILD), the presence of a usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy (SLB), or specific combinations of HRCT and SLB patterns in patients subjected to SLB [1]. International guidelines for the diagnosis and management of IPF have highlighted the importance of involving a multidisciplinary team composed of a pulmonologist, a radiologist and a pathologist for diagnosing the disease. This approach has been shown to increase the accuracy of IPF diagnosis [25].

IPF diagnosis can be challenging due to the nonspecific nature of the presenting symptoms, the complicated diagnostic process and the rarity of the disease, often associated with a lack of IPF diagnostic experience. As a result, diagnosis is often incorrect or delayed [26,27], which either leads to delayed initiation of an efficacious treatment, or even results in commencing ineffective or harmful interventions, leading to worse outcomes [28].

Improving early diagnosis is key to achieving timely referral to a specialized center to establish the diagnosis, ruling out differential diagnoses (especially chronic hypersensitivity pneumonitis, idiopathic nonspecific interstitial pneumonia, and ILD related to connective tissue disease), and initiating discussions on potential lung transplantation. Early and accurate diagnosis is a prerequisite to initiation of treatment with approved agents able to slow disease progression, which is the best attainable goal for a progressive, irreversible and fatal disease such as IPF [29]. To achieve best outcomes, it is likely that early treatment intervention may be beneficial once clinical or physiological impairment of lung function is evidenced [3,26,30,31].

Treatment

There is currently no cure for IPF and treatment options are limited. Best supportive care and

nonpharmacological disease management may include oxygen therapy, pulmonary rehabilitation, antireflux therapy, palliative care and lung transplantation in patients fulfilling established selection criteria [32]. Oral corticosteroids and immunosuppressive therapy are no longer initiated in patients with a definite diagnosis of IPF. Pharmacological agents are scarce and several candidates have failed to demonstrate treatment efficacy in clinical trials (for a more detail overview of completed IPF clinical trials, the reader is referred to a recent review by Antoniou *et al.* [33]). Given the progressive and irreversible nature of the disease, the current treatment goal of pharmaceutical interventions is to slow disease progression and relieve symptoms [29].

Pirfenidone

Overview of pirfenidone

Pirfenidone is the first and only approved treatment for adult patients with mild to moderate IPF. Pirfenidone was approved in Japan in 2008, in the European Union in 2011 and in Canada in 2012. It is commercially available under the trade name Esbriet® (InterMune) in 13 European countries (Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Luxembourg, Norway, Sweden and the UK). In many European countries, pirfenidone is currently the first-line treatment for adult patients with mild to moderate IPF [34]. Pirfenidone is marketed in Japan and South Korea as Pirespa® (Shionogi & Co. Ltd) and also under different trade names in India, China and Argentina. A Phase III clinical trial, ASCEND (PIPF016 [NCT01366209]), was requested by the US FDA and is currently ongoing to support regulatory registration in the USA [35].

Pirfenidone, or 5-Methyl-1-phenyl-2-(1H)-pyridone (Figure 2), is an orally active, small molecule, the primary antifibrotic activity of which is supplemented by additional anti-inflammatory properties [35]. The first report of pirfenidone's antifibrotic effects in animals dates back to 1982 [36], while the first clinical use in pulmonary fibrosis did not occur until a decade later [37].

The antifibrotic, anti-inflammatory and antioxidant properties of pirfenidone have been demonstrated across multiple *in vitro* and *in vivo* animal models, in more than 40 publications and reports (for a detailed review, the reader is referred to Schaefer *et al.* [35]). Pirfenidone's antifibrotic activity is considered to result from its ability to reduce the production of profibrotic cytokines such as TGF-β [38–40] and basic fibroblast growth factor (bFGF) [39], to attenuate the expression, synthesis and/or accumulation of collagen [41], and to inhibit the recruitment and/or expression of extracellular matrix-producing cells (i.e., fibroblasts) [42]. Pirfenidone-mediated reduction of pro-inflammatory cytokine

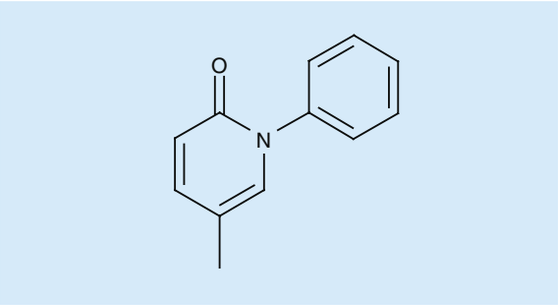

Figure 2. Pirfenidone or 5-methyl-1-phenyl-2-(1H)-pyridone.

production, including TNF-α and several interleukins, as well as reduced accumulation of inflammatory cells in response to stimuli accounts for pirfenidone's anti-inflammatory effects [43–45]. The protective anti-oxidant effects of pirfenidone are associated with its modulation of oxidative stress [46].

In vivo animal models have provided the greatest insights into pirfenidone's antifibrotic properties across multiple organ systems, in both prophylactic and therapeutic dosing regimens and at clinically relevant doses. Pirfenidone administration was also shown to significantly reduce transplant-related pulmonary fibrosis and prevent loss of pulmonary function in a model of post-transplant obliterative bronchiolitis [38]. Moreover, cell-based studies are supportive of the effects observed *in vivo* [35].

Oral administration of pirfenidone results in rapid absorption, high bioavailability and broad distribution. Following oral administration with food, as recommended in the Summary of Product Characteristics [47], pirfenidone is slowly absorbed and reaches the maximum plasma concentration (C_{max}) after 2.5–4 h [48]. Administration with food reduces C_{max} by 50%, with little effects on overall exposure [48]. The mean apparent terminal elimination half-life is 2.4 h in healthy volunteers [48]. Following an initial 2-week titration period, the recommended maintenance dose is three 267 mg capsules three times daily with food for a total of 2403 mg/day [47]. Administration with food was shown to reduce the incidence of adverse events (AEs) such as nausea and dizziness [47].

Pirfenidone is mainly metabolized by CYP1A2 (accounting for approximately 70–80%), with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1 [47]. Approximately 80% of an orally administered dose of pirfenidone is excreted in urine within 24 h, mainly in the form of the major metabolite 5-carboxy-pirfenidone (>95% of that recovered), with less than 1% of pirfenidone excreted unchanged in urine [48]. *In vitro* and *in vivo* studies to date have not detected any activity of the

major metabolite 5-carboxy-pirfenidone, although a recent report pointed out the possible involvement of 5-hydroxypirfenidone and 5-carboxy-pirfenidone metabolites in the antifibrotic action of pirfenidone as therapeutic agent for IPF [49].

Pirfenidone should be used with caution in patients with mild to moderate hepatic impairment, as drug exposure in this patient population was shown to be increased by a mean of 60% [47]. It is also recommended that these patients be closely monitored for signs of toxicity, especially if they are concomitantly taking a CYP1A2 inhibitor [47]. Pirfenidone is contraindicated in patients with severe hepatic impairment and end-stage liver disease [47]. No dose adjustment is required in patients with mild to moderate renal impairment. Pirfenidone is contraindicated in patients with severe renal impairment (creatinine clearance rate of less than 30 ml/min) or end-stage renal disease requiring dialysis [47].

Pirfenidone is contraindicated in patients concomitantly treated with strong CYP1A2 inhibitors such as fluvoxamine. Concomitant treatment of pirfenidone and other inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone should be avoided [47]. If concomitant use of pirfenidone with a strong and selective inhibitor of CYP1A2 (e.g., enoxacin) cannot be avoided, the dose should be reduced to 801 mg daily and patients should be closely monitored. If ciprofloxacin at the dose of 750 mg twice daily cannot be avoided, pirfenidone dose should be reduced to 1602 mg/day. Pirfenidone should be used with caution in patients treated with other moderate inhibitors of CYP1A2 (e.g., amiodarone, propafenone). Co-administration of potent inducers of both CYP1A2 and the other CYP isoenzymes involved in the metabolism of pirfenidone (e.g., rifampicin) should be avoided whenever possible [47]. A Phase I study showed that the exposure to pirfenidone in smokers was 50% of that observed in non-smokers. Concomitant use of strong inducers of CYP1A2 including smoking should be avoided during pirfenidone therapy based on the observed relationship between cigarette smoking and its potential to induce CYP1A2. Patients should be encouraged to discontinue use of strong inducers of CYP1A2 and to stop smoking before and during treatment with pirfenidone [47].

Pirfenidone in clinical trials

The efficacy and safety of pirfenidone for the treatment of IPF has been extensively evaluated in clinical trials (Table 1) [37,50–52].

Efficacy profile

The first use of pirfenidone in clinical trials was in an open-label, compassionate use trial involving 54 patients with advanced IPF [37]. This study showed that pirfenidone was well tolerated and had the potential to stabilize lung function.

Following the encouraging results of this early study, pirfenidone was further investigated in a randomized, double-blind, placebo-controlled trial in 107 Japanese patients with IPF [50]. The study was prematurely stopped following a planned interim analysis at 24 weeks, which showed an increased incidence of acute exacerbations among patients randomized to the placebo arm. The decline in vital capacity (VC) at 36 weeks was significantly reduced in patients treated with pirfenidone as compared with placebo [50].

A subsequent randomized, double-blind, placebo-controlled Phase III trial in 275 Japanese patients with IPF showed that pirfenidone (1800 mg/day) significantly reduced the decline in VC at week 52 ($p = 0.042$) and improved progression-free survival (PFS; $p = 0.028$) [52].

Pirfenidone was further evaluated in two large, nearly identical multinational, randomized, double-blind, placebo-controlled, Phase III trials (PIPF004; n = 435 [NCT00287716], and PIPF006; n = 344 [NCT00287729]) [51]. In PIPF004, patients with mild to moderate IPF were randomized to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, or placebo in a 2:1:2 ratio, while in PIPF006 patients were assigned to pirfenidone 2403 mg/day or placebo in a 1:1 ratio. In PIPF004, the primary end point (absolute change in percentage predicted forced VC [FVC] at week 72) was met (35% relative reduction; -8.0 vs -12.4% in the pirfenidone 2403 mg/day and placebo groups, respectively; $p = 0.001$), and PFS time (defined as time to confirmed ≥10% decline in percentage predicted FVC, ≥15% decline in percentage predicted diffusing capacity of the lung for carbon monoxide [DLco] or death) was improved (hazard ratio [HR]: 0.64; 95% CI: 0.44–0.95; $p = 0.023$). In PIPF006, the primary end point was not met (-9.0 vs -9.6% in the pirfenidone and placebo groups, respectively; $p = 0.501$), although a significant pirfenidone treatment effect was observed at weeks 24 ($p < 0.001$), 36 ($p = 0.011$), 48 ($p = 0.005$) and in analysis of all study timepoints ($p = 0.007$). A pooled analysis of PIPF004 and PIPF006 including patients treated with pirfenidone 2403 mg/day (n = 345) and placebo (n = 347) showed a significant pirfenidone treatment effect in the mean change in percentage predicted FVC (-8.5 vs -11.0%, respectively; $p = 0.005$; 2.5% absolute reduction; 22.8% relative reduction), categorical change of ≥10% FVC decline (21 vs 31%, respectively; $p = 0.003$), mean change in 6-min walk test distance (-52.8 vs -76.8 m, respectively; $p < 0.001$; 24 m absolute difference; 31% relative difference) and PFS time (HR: 0.74; 95% CI: 0.57–0.96; $p = 0.025$) [51]. The magnitude of treatment effect was overall clin-

Table 1. Overview of pirfenidone clinical trials.

Clinical trial number	Study design	Treatment arms and dosing regimen	Patients (n)	Primary end point	Ref.
NA	Phase II, open-label, compassionate use	Pirfenidone 3600 mg/day	54	Overall survival and measurable change in lung function after 12 months	[37]
NA	Phase II, double-blind, placebo controlled	Pirfenidone 1800 mg/day (n = 72) Placebo (n = 35)	107	Change in 6MET SpO_2 from baseline to week 48	[50]
JAPICCTCI-050121	Phase III, randomized, double-blind, placebo-controlled	Pirfenidone 1800 mg/day (n = 110) Placebo (n = 109) Pirfenidone 1200 mg/day (n = 56)	275	Change in VC from baseline to week 52	[52]
PIPF004 (NCT00287716)	Phase III, randomized, double-blind, placebo-controlled	Pirfenidone 2403 mg/day (n = 174) Placebo (n = 174) Pirfenidone 1197 mg/day (n = 87)	435	Absolute change in percent predicted FVC from baseline to week 72	[51]
PIPF 006 (NCT00287729)	Phase III, randomized, double-blind, placebo-controlled	Pirfenidone 2403 mg/day (n = 171) Placebo (n = 173)	344	Absolute change in percent predicted FVC from baseline to week 72	[51]

6MET: 6-min exercise test; FVC: Forced vital capacity; NA: Not available; SpO_2: Blood oxygen saturation; VC: Vital capacity.

ically meaningful [10,53,54] and consistent across multiple clinically meaningful outcomes. Although the trials were not powered to assess mortality, fewer overall deaths (19 [6%] vs 29 [8%]) and fewer IPF-related deaths (12 [3%] vs 25 [7%]) occurred in the pirfenidone 2403 mg/day groups than in the placebo groups [51]. However, data from a small retrospective Japanese study did not support a beneficial effect of pirfenidone on survival [55].

An independent Cochrane Collaboration meta-analysis including the two CAPACITY studies and the Japanese Phase III study (n = 1046) showed that pirfenidone significantly improved PFS time (HR: 0.70; 95% CI: 0.56–0.88; p = 0.002) [56]. The magnitude of PFS benefit in IPF, which is similar to that observed in non-small-cell lung cancer trials, is considered as clinically meaningful and should be regarded as a successful outcome [10].

The long-term treatment of pirfenidone is being further evaluated in the RECAP study (PIPF012, NCT00662038), an open-label extension study in patients with IPF who completed either of the CAPACITY trials, regardless of their original treatment assignment. A total of 603 patients were enrolled, of whom 178 were newly treated with pirfenidone at a dosage of 2403 mg/day and had baseline lung function values that met CAPACITY inclusion criteria [57]. The proportion of patients experiencing 10% or more FVC decline at week 60 was 16.6%, compared with 16.8 and 24.8% in the pirfenidone and placebo arms of the pooled CAPACITY trials, respectively [57].

Pirfenidone's effects on slowing lung function decline can be assessed by CT scan. A retrospective study on 38 patients treated with pirfenidone and 40 age-matched controls showed that a significantly higher proportion of patients treated with pirfenidone versus placebo had stable disease based on pulmonary function tests (71.1 vs 37.5%, respectively; p = 0.035) and changes on CT (63.2 vs 30%, respectively; p = 0.006). The changes in CT evaluated by the radiologists significantly correlated with the change in VC [58]. This study suggests that CT imaging can be considered as an additional tool to assess the outcome of pirfenidone therapy in patients with IPF [58].

A small retrospective study in 18 Japanese patients suggested that pirfenidone therapy can decrease the rate

of FVC decline in patients with advanced-stage IPF and progressive disease, defined as patients experiencing ≥10% relative decline in FVC within the 6 (±2) months preceding enrollment (Table 2) [59].

Safety & tolerability profile

Pooled tolerability data from patients (n = 345) who received pirfenidone at the recommended maintenance dose of 2403 mg/day in the CAPACITY trials PIPF004 and PIPF006 showed that pirfenidone has an acceptable tolerability profile [51].

The majority of AEs were mild to moderate in gravity, reversible, and resolved with continued use, dose adjustment or treatment discontinuation (temporary or permanent). The most common treatment-emergent AEs were nausea (36%), rash (32%), dyspepsia (19%), vomiting (14%) and photosensitivity reactions (12%) [51]. The incidence of nausea, dyspepsia and skin-related AEs seemed to be dose related, with numerically lower values in patients receiving pirfenidone 1197 mg/day. Hepatic enzyme elevations occurred more frequently in patients treated with pirfenidone 2403 mg/day. The incidence of alanine aminotransferase or aspartate aminotransferase elevations of more than three-times the upper limit of normal in the pooled group of patients treated with pirfenidone 2403 mg/day was 4.1% as opposed to 0.6% in the placebo group; however, these were relatively uncommon and not associated with untoward safety consequences. Change in laboratory parameters from baseline to week 72 were similar across treatment groups except for γ-glutamyl transferase (mean increase of 7.6 vs 0.0 U/l for patients randomized to pirfenidone 2403 mg/day vs placebo, respectively) and creatinine (mean decrease of 5.6 vs 1.1 µmol/l for patients randomized to pirfenidone 2403 mg/day vs placebo, respectively) [60]. Study discontinuation as a result of AEs occurred in 15 versus 9% of patients randomized to pirfenidone 2403 mg/day versus placebo, respectively.

A meta-analysis of randomized controlled trials analyzing the AEs of pirfenidone for the treatment of pulmonary fibrosis confirmed that gastrointestinal (GI) and skin-related AEs were more common in the group of patients receiving pirfenidone as opposed to placebo, highlighting the need for appropriate precaution [61].

The long-term safety of pirfenidone has been assessed in an analysis including 789 patients from the CAPACITY studies (PIPF004 and PIPF006), RECAP (PIPF012) and a compassionate use study in the USA (PIPF002). The median duration of pirfenidone exposure was 2.6 years (1 week to 7.7 years), with a cumulative total exposure of 2052 person exposure years [62]. Consistent with previous studies, GI and skin-related AEs were the most commonly reported AEs, specifically nausea (40%), dizziness (38%), rash (26%), dyspepsia (21%) and vomiting (18%). These were generally mild to moderate and rarely led to treatment discontinuation.

Pirfenidone-related GI & skin-related AEs

Animal studies have suggested that the underlying mechanisms of pirfenidone-related GI AEs may be related to its effect on reducing the rate of gastric emptying and small intestinal transit [63]. In healthy adult subjects, it was demonstrated that co-administration with food decreased the rate and extent of pirfenidone absorption, with data also suggesting that food intake reduces the risk of GI-related AEs, thereby improving overall tolerability [48].

Pirfenidone-related skin photosensitivity reactions are likely related to the drug's absorbance of UV light, both UVA and UVB [64]. *In vitro* studies have shown that absorption of UV light by pirfenidone at physiologically relevant concentrations leads to the generation of reactive oxygen species and lipid peroxidation [64], which may account for the skin-related AEs of pirfenidone. Preclinical studies suggest that pirfenidone-related skin AEs are reversible and proportional to UV exposure and the drug's concentration [65].

Prevention & management of GI & skin-related AEs

To prevent and help mitigate the incidence of some GI AEs, such as nausea, it is recommended to take pirfenidone with a meal, as food intake decreases the C_{max} by 50% [47]. Taking each of the three capsules separately throughout the meal rather than simultaneously may help mitigate GI AEs [66,67]. This recommendation is supported by results from preclinical studies showing that pirfenidone-associated GI discomfort is mostly related to reduction in gastric motility and is linked to the peak plasma concentration of pirfenidone; splitting pirfenidone doses may partially alleviate the drug-mediated reduction of gastric motility [68]. Dose reduction to one to two capsules, two to three times per day can be employed to reduce the incidence of GI AEs [47]. If symptoms persist, patients may be instructed to interrupt treatment for 1–2 weeks to allow symptoms to resolve. Once symptoms have resolved or become tolerable, pirfenidone can be re-introduced up to the recommended daily dose as tolerated [47].

Measures that can help prevent or reduce the extent of skin-related AEs include taking pirfenidone with a meal, avoiding sun exposure as much as possible, frequently and generously applying sunscreens with a high sun protection factor and a high UVA and UVB protection grade and wearing protective clothing [66,67]. In cases of mild to moderate photosensitivity reaction or rash, pirfenidone dose may be reduced to three capsules

Table 2. Real-life clinical experiences with pirfenidone published in 2013.

Study	Country	Patient (n)	Mean age (years)†	Baseline FVC (% predicted)†	Efficacy outcome	GI AEs (n)	Skin-related AEs (n; %)	Therapy discontinuation due to AEs (n; %)	Ref.
Bonella *et al.*	Germany	45	69 ± 7	61 ± 15	Stable lung function in 28/40 (70%) patients; subjective improvement in cough in 12/36 (33%) patients	17 (38%)	10 (22)	6 (13%)	[69,70]
Oltmanns *et al.*	Germany	60	70 (63–74)	68 (58–80)‡	The majority of patients treated with pirfenidone showed stable disease	NA	NA	8 (13%)	[71]
Chaudhuri *et al.*	UK	40	65.8 (48–80)	65.8 (48–80)	Reduction in FVC and TLco decline at 9 months	87%	10.3%§	6 (15%)	[66]
Ravaglia *et al.*	Italy	81¶	69 (41–81)	70.8	Following treatment, lung function was stable or significantly improved in 40/68 (59%) patients	NA	NA	13 (16%)	[74]
Nieto Barbero *et al.*	Spain	86	NA	70 ± 19	No significant decline in FVC and DLco between baseline and follow-up among subjects who had repeated pulmonary function testing (n = 20)	35 (41%)	11 (13%)#	12 (14%)	[75]
Okuda *et al.*	Japan	76	70.5 ± 8.3	65.3 ± 16.1	Reduction in FVC and DLco decline	18 (24%)††	19‡‡ (25)	18.4%	[72]
Arai *et al.*	Japan	41	60 (65.5–75.5)	66.7 (54.8–77.8)‡	Significant reduction in VC decline in patients with severity grade I/II (p = 0.0039)	24 (59%)§§	5 (12)#	6 (15%)	[73]

†Reported as mean ± SD or mean (range) where available.
‡Percent predicted VC.
§Rash.
¶A total of 81 patients were treated with pirfenidone but only 68 were included in the study as 13 patients had discontinued the drug in the first 3 months because of AEs.
#Photosensitivity.
††Gastric distress (n = 9) and nausea (n = 9).
‡‡Photosensitivity (n = 14) and rash (n = 5).
§§Anorexia and/or nausea.
AE: Adverse events; DLco: Diffusion capacity of the lung for carbon monoxide; FVC: Forced vital capacity; GI: Gastrointestinal; TLco: Transfer lung factor for carbon monoxide; VC: Vital capacity.

per day. If the rash persists after 7 days, pirfenidone should be discontinued for 15 days, with re-escalation according to the initial 2-week titration regimen to the recommended daily dose as tolerated [47]. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt treatment and to seek medical advice [47].

Further experience with pirfenidone in clinical practice

This section summarizes recent data obtained from real-life experience with pirfenidone in clinical practice (Table 2).

Germany

A total of 45 patients with mild to moderate IPF were treated with pirfenidone in the Ruhrlandklinik Hospital in Essen, Germany [69]. At the end of the follow-up period, lung function (measured by change in FVC) had stabilized in 28 of the 40 patients who had treatment duration greater than 3 months (70%) [69]. The proportion of patients (n = 23) with ≥5% FVC reduction after 6 months of therapy was significantly lower than before therapy (26 vs 78%; p = 0.018) [69]. Cough was subjectively improved in 12/36 (33%) patients under pirfenidone treatment [70]. The most frequently observed AEs were GI (17/45; 38%) and skin related (10/45; 22%). Pirfenidone treatment discontinuation due to AEs occurred in 6/45 (13%) patients (Table 2). Overall, pirfenidone was generally well tolerated and its tolerability profile was consistent with that previously published [69].

In a German tertiary referral center for ILD, 60 patients with IPF started pirfenidone therapy [71]. Disease progression, which was defined as a reduction of VC ≥10% or diffusion capacity (DLco) ≥15%, was observed in seven (12%) patients. The majority of patients showed stable disease. AEs occurred in 38 (66%) patients; eight (13%) patients discontinued therapy due to AEs (Table 2). Pirfenidone's efficacy and safety profile was consistent with data published in the literature; the drug was overall well tolerated and AEs were manageable [71].

United Kingdom

The real-life experience with pirfenidone in 40 patients with IPF involved in a Named Patient Program (NPP) in a specialized center in Manchester, UK, has recently been published [66]. At 9 months, a difference in gradient of FVC decline before and after pirfenidone treatment initiation of -1.043 ± 1.605 versus -0.197 ± 0.231, respectively, was observed (n = 15) [66]. AEs were experienced by 23/40 (58%) patients, with GI and rash accounting for 87 and 10% of all AEs, respectively (Table 2) [66]. Treatment discontinuation rates dropped from an initial 15 (6/40) to 0% in the subsequent 10 months thanks to regular specialist nurse and clinical review, support and patient education [66]. Despite some major limitations (i.e., the retrospective and observational nature of the study with small patient numbers, the lack of appropriate controls and the incomplete collection of pulmonary function data), this report shows that pirfenidone is well tolerated and that treatment adherence can be improved by regular specialist nurse support and patient education [66].

Japan

In a recent study published by Okuda *et al.* [72], 76 patients with mild-to-severe IPF were treated with pirfenidone (mean ± SD percent predicted baseline FVC was 65.3 ± 16.1; Table 2). Upon pirfenidone therapy, FVC decline was improved from -188 ml during the 6-month period prior to therapy initiation to -19 ml during the 6-month period after therapy GI and skin-related AEs occurring in 18 (24%) and 19 (25%) patients, respectively (Table 2). Consistent with data from clinical trials, pirfenidone was well tolerated and had beneficial effects in reducing lung function decline [72].

In another recent Japanese study, Arai *et al.* reported the clinical experience with pirfenidone in 41 patients with severity grades ranging from I to IV as defined by the Japanese Respiratory Society [73]. Pirfenidone treatment led to a significant reduction in VC decline in patients with severity grade I/II (n = 10; p = 0.0039). Anorexia and/or nausea occurred in 24 (59%) patients while photosensitivity reactions were reported in five (12%) patients (Table 2) [73].

Italy

The clinical practice experience with pirfenidone in 68 patients in a specialized center in Forlí, Italy, showed that treatment stabilized or even improved lung function in 40 (59%) patients. Pirfenidone was generally well tolerated and the results were in line with previously published safety and efficacy data on pirfenidone (Table 2) [74].

Spain

A total of 86 patients with IPF and mean ± SD percent predicted FVC of 70 ± 19 were treated with pirfenidone in the context of the NPP (Table 2) [75]. Among subjects who underwent repeated pulmonary function testing (n = 20), no significant decline in FVC and DLco was observed between baseline and follow-up, supporting the beneficial effects of pirfenidone in slowing disease progression. GI and photosensitivity were the most commonly reported AEs, occurring in 35 (41%) and 11 (13%) patients, respectively. In conclusion, the results of

the real-life experience with pirfenidone in the Spanish NPP are in line with previously published clinical trial data [75].

The Netherlands

In the Netherlands, a preliminary evaluation of the effects of pirfenidone on cough was conducted in 23 patients using a nonvalidated clinical cough score based on a scale from 1 (no cough) to 10 (worst cough) [76]. The mean baseline cough score was 5.4; data were not corrected for intercurrent respiratory tract infections. After 1 month, cough was decreased in 12/23 (52%) patients (mean reduction of 2.1 units), it remained unchanged in seven (30%) and increased in four patients (17%; +1.7). After 6 months of pirfenidone treatment, data were available in 13 patients; the cough score was reduced by 2 units in nine (69%) of those patients, suggesting that pirfenidone may have potential benefit in reducing cough [76]. The encouraging preliminary results of pirfenidone on cough warrant further investigation.

Report on patients' perspectives

To explore patients' perceptions of current therapy and management of IPF (specifically pirfenidone as the first approved treatment for IPF), a qualitative survey was conducted in 45 patients with IPF (mean age 68.5 years) [77]. Post diagnosis, a total of 68% of patients felt that their knowledge about disease severity, treatment options and prognosis markedly increased, predominantly through the use of electronic media. Transition to oxygen therapy had a profound impact on patients' quality of life and was associated with social exposure of the disease, often with feelings of shame (35%), and with impaired emotional well-being. An overwhelming lack of psychological support was felt by 79% of patients struggling to comprehend the disease process, thus emphasizing the need to improve communication in the consultation and increase provision of psychological support, especially when prescribing oxygen therapy. Pirfenidone was well tolerated and was perceived to bring hope to the majority of patients (83%). A need for improving early diagnosis and standardizing access to information and therapies was identified [77].

Conclusion & future perspective

IPF is an irreversible, inexorably progressive and eventually fatal disease. As the best attainable treatment goal for IPF is slowing disease progression [29], timely initiation of therapy might be determinant regarding long-term outcomes. To date, pirfenidone is the only approved and commercially available treatment (in a number of countries) for adult patients with mild to moderate IPF that has been shown to reduce FVC decline [47]. Since FVC decline has been shown to correlate with increased risk of mortality [53], further effort should be made towards achieving earlier diagnosis and starting treatment intervention at earlier stages, when lung function decline has not progressed too far. According to a recent review by Cordier and Cottin, lung biopsy to confirm IPF diagnosis should be discussed during the early 'honeymoon' phase of IPF, when crackles can already be heard at pulmonary auscultation with only subtle HRCT abnormalities and mostly preserved lung function (subclinical ILD) [31]. In support for earlier initiation of pirfenidone therapy, it has been shown that patients with stable/minimal disease progression also benefit from pirfenidone treatment [60]. Given the progressive, irreversible and fatal course of the disease, the authors believe that treatment should be initiated as soon as symptoms are present and pulmonary function is impaired or deteriorates in subjects with interstitial lung abnormalities detected on HRCT and with a diagnosis of IPF. There is currently no consensus regarding when treatment should be discontinued (other than guided by tolerability issues). Robust data are needed in order to determine the optimal timing for initiation and potential discontinuation of IPF drug therapy.

Besides its demonstrated effects on reducing lung function decline, preliminary data from real-life clinical practice experience in individual centers in the Netherlands, Germany and Italy have suggested a potential beneficial effect of pirfenidone on cough, warranting further investigations. An observational, open-label clinical study to assess the effect of pirfenidone background therapy on cough and other measures of quality of life has been started in three centers (the Netherlands, Italy and France; NCT02009293). A total of 50 patients are planned to be recruited for a treatment duration of 3 months.

Pirfenidone safety and tolerability is also planned to be evaluated in patients with systemic sclerosis-related ILD in a Phase II, multinational, open-label, randomized, parallel-group study (LOTUSS; NCT01933334). Participants are currently being recruited and will be randomized to receive pirfenidone for 16 weeks either according to the standard (2 weeks) or slower titration schedule (4 weeks), before reaching the recommended daily dose of 2403 mg.

Novel pirfenidone formulations may help improve patient compliance by lowering dosing frequency and reducing dosing, which is expected to reduce AEs. A preclinical study showed that weekly intra-tracheal administration of pirfenidone nanoparticles can lead to sustained drug delivery to the lungs and enhance the effect on reducing bleomycin-induced pulmonary fibrosis in mice [78], suggesting that further effort in developing targeted pirfenidone delivery may improve

both pirfenidone's efficacy and safety profile. Results from another preclinical study in rats showed that an inhalable powder formulation of pirfenidone was associated with reduced phototoxic AEs and may represent an alternative to oral pirfenidone [79]. However, clinical studies are needed to assess the efficacy and safety profile of inhaled pirfenidone for the treatment of pulmonary fibrosis.

In the first half of 2014, the results of three important clinical trials in IPF will be expected that may profoundly change the IPF landscape and may provide further treatment options to affected patients:

- An additional Phase III study, ASCEND, has been requested by the FDA to obtain pirfenidone approval in the USA. Results of this study are expected in the second quarter of 2014;

- Nintedanib is an investigational oncology compound with anti-angiogenic properties that inhibits tyrosine kinases of several growth factor receptors, including the PDGF, VEGF and FGF receptors. As these receptors are involved in the process of fibrogenesis [80], nintedanib has been investigated as a potential treatment for IPF in a Phase II study (TOMORROW; NCT00514683) [81]. The results of two identical multicenter Phase III trials (INPULSIS™ 1 and 2; NCT01335477 and NCT01335464) assessing the efficacy and safety of nintedanibare expected in early 2014;

- NAC, either alone or in combination with prednisone and azathioprine (triple therapy) has been widely used off-label for the treatment of IPF, although there is no definitive evidence for its efficacy. In the PANTHER-IPF study (NCT00650091) aiming at evaluating the safety and efficacy of triple therapy, patients were randomized to one of three arms (three-drug combination, NAC alone or placebo) [82]. Following a planned mid-point interim analysis, the combination therapy arm was discontinued due to an excess number of deaths, hospitalizations and serious AEs compared with the placebo arm [82]. The trial is still ongoing for the NAC monotherapy and placebo arms, with results expected in early 2014.

Given the complex pathophysiology of IPF involving multiple mechanistic pathways [83] and in recognition of the common pathogenic pathways shared by IPF and cancer [11], a pleiotropic oncology-like treatment approach based on multiple agents with different mechanisms of action (combination therapy) will most likely represent the way of treating patients with IPF in the future [33,84]. Preliminary results from a small retrospective study in Japanese patients (n = 18) receiving pirfenidone therapy as monotherapy or in combination with inhaled NAC suggested that combined therapy may have favorable outcomes [59]; however, further studies are needed. A study assessing the safety and tolerability of NAC in patients with IPF with background treatment of pirfenidone is currently ongoing (PANORAMA study, EudraCT number 2012–000564–14).

The upcoming results of the ASCEND, INPULSIS™-1 and 2 and PANTHER-IPF trials in the first half of 2014 will likely change the current practice of IPF management. Based on the new evidence that will soon become available, an updated official statement from the American Thoracic Society and European Respiratory Society on the guidelines for IPF diagnosis and management is awaited.

The role of patients and/or patient representatives in the development of guidelines and official documents on the disease is becoming increasingly recognized. In Europe, the task force 'European Lung Foundation' has been launched by the European Respiratory Society to involve patient associations in the production of IPF diagnosis and treatment documents. Moreover, the recent European Advancing in Idiopathic pulmonary fibrosis Research meeting that took place in November 2013 in Nice, France, brought together for the first time leading IPF experts, European clinicians, researchers and patient associations to share best practice and improve knowledge on this fatal disease, as well as to bring new hope for patients with IPF.

Despite being a rare disease of unknown cause, the IPF community has witnessed much progress in the last decade. Approval of pirfenidone and the development of other promising compounds for the treatment of IPF have given some hope to patients to slow the progression of this deadly disease.

Financial & competing interests disclosure

V Cottin has received speaker honoraria and travel grants for medical congresses from Boehringer Ingelheim, Gilead and InterMune. M Wijsenbeek has received speaker and advisory board honoraria from InterMune and Boehringer Ingelheim (paid to the Institution). F Bonella has received speaker honoraria and travel grants for medical congresses from Boehringer Ingelheim, Gilead and InterMune. C Vancheri has received speaker and advisory board honoraria from InterMune and Boehringer Ingelheim. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by Dominique Spirig (InterMune International AG, Switzerland).

Executive summary

- Idiopathic pulmonary fibrosis (IPF) is a rare, progressive, irreversible and ultimately fatal fibrotic lung disease with a median survival of only approximately 3 years.
- Pirfenidone, an antifibrotic agent with anti-inflammatory properties, is the first and only approved therapy in the European Union indicated for reducing lung function decline in adult patients with mild to moderate IPF.
- An independent Cochrane meta-analysis of three Phase III clinical trials showed that pirfenidone reduces the risk of disease progression by 30%.
- Pirfenidone is generally well tolerated, with the most common treatment-emergent adverse events being gastrointestinal and dermatologic in nature. These can be prevented and/or mitigated by taking pirfenidone with food (preferentially in split doses), avoiding sun exposure, wearing protective clothing and regularly applying sunscreen.
- Since its approval in Japan and the European Union, experience with pirfenidone in clinical trials and real-life clinical practice has accumulated. Consistent with clinical trial data, pirfenidone is generally well tolerated in real-world settings and has the potential to reduce lung function decline.
- In the first half of 2014, the results of three important clinical trials in IPF will be expected that may profoundly change the IPF landscape and may provide further treatment options to affected patients.

References

Papers of special note have been highlighted as:

- • **of interest**
- •• **of considerable interest**

1 Raghu G, Collard HR, Egan JJ *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am. J. Respir. Crit. Care Med.* 183(6), 788–824 (2011).

•• **Official ATS/ERS/JRS/ALAT statement on the diagnosis and management of idiopathic pulmonary fibrosis.**

2 Orphanet. Prevalence of rare diseases: bibliographic data. *Orphanet Report Series Rare Disease Collection* 1 (2013).

3 American Thoracic Society and European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am. J. Respir. Crit. Care Med.* 161(2 Pt 1), 646–664 (2000).

4 Navaratnam V, Fleming KM, West J *et al.* The rising incidence of idiopathic pulmonary fibrosis in the UK. *Thorax* 66(6), 462–467 (2011).

5 Copley SJ, Wells AU, Hawtin KE *et al.* Lung morphology in the elderly: comparative CT study of subjects over 75 years old versus those under 55 years old. *Radiology* 251(2), 566–573 (2009).

6 Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *Eur. Respir. Rev.* 21(126), 355–361 (2012).

7 Bjoraker JA, Ryu JH, Edwin MK *et al.* Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 157(1), 199–203 (1998).

8 Collard HR, King TE, Jr., Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 168(5), 538–542 (2003).

9 Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. *Orphanet J. Rare Dis.* 3, 8 (2008).

10 Vancheri C, Du Bois RM. A progression-free end-point for idiopathic pulmonary fibrosis trials: lessons from cancer. *Eur. Respir. J.* 41(2), 262–269 (2013).

11 Vancheri C. Common pathways in idiopathic pulmonary fibrosis and cancer. *Eur. Respir. Rev.* 22(129), 265–272 (2013).

• **Highlights the similarities between idiopathic pulmonary fibrosis and cancer.**

12 Verdecchia A, Francisci S, Brenner H *et al.* Recent cancer survival in Europe: a 2000–2002 period analysis of EUROCARE-4 data. *Lancet Oncol.* 8(9), 784–796 (2007).

13 Cottin V, Cordier JF. Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis? *Eur. Respir. J.* 40(3), 519–521 (2012).

14 Kim DS, Collard HR, King TE, Jr. Classification and natural history of the idiopathic interstitial pneumonias. *Proc. Am. Thorac. Soc.* 3(4), 285–292 (2006).

15 King TE, Jr., Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet* 378(9807), 1949–1961 (2011).

16 Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 183(4), 431–440 (2011).

17 Fingerlin TE, Murphy E, Zhang W *et al.* Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat. Genet.* 45(6), 613–620 (2013).

18 Lawson WE, Grant SW, Ambrosini V *et al.* Genetic mutations in surfactant protein C are a rare cause of sporadic cases of IPF. *Thorax* 59(11), 977–980 (2004).

19 Mushiroda T, Wattanapokayakit S, Takahashi A *et al.* A genome-wide association study identifies an association of a common variant in TERT with susceptibility to idiopathic pulmonary fibrosis. *J. Med. Genet.* 45(10), 654–656 (2008).

20 Peljto AL, Zhang Y, Fingerlin TE *et al.* Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA* 309(21), 2232–2239 (2013).

21 Seibold MA, Wise AL, Speer MC *et al.* A common MUC5B promoter polymorphism and pulmonary fibrosis. *N. Engl. J. Med.* 364(16), 1503–1512 (2011).

22 Garcia-Sancho C, Buendia-Roldan I, Fernandez-Plata MR *et al.* Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. *Respir. Med.* 105(12), 1902–1907 (2011).

23 Selman M, King TE, Pardo A, American Thoracic S, European Respiratory S, American College of Chest P. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann. Intern. Med.* 134(2), 136–151 (2001).

24 Selman M, Pardo A. Role of epithelial cells in idiopathic pulmonary fibrosis: from innocent targets to serial killers. *Proc. Am. Thorac. Soc.* 3(4), 364–372 (2006).

25 Flaherty KR, King TE Jr., Raghu G *et al.* Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am. J. Respir. Crit. Care Med.* 170(8), 904–910 (2004).

26 Du Bois RM. An earlier and more confident diagnosis of idiopathic pulmonary fibrosis. *Eur. Respir. Rev.* 21(124), 141–146 (2012).

27 Spagnolo P, Tonelli R, Cocconcelli E, Stefani A, Richeldi L. Idiopathic pulmonary fibrosis: diagnostic pitfalls and therapeutic challenges. *Multidiscip. Respir. Med.* 7(1), 42 (2012).

28 Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. *Am. J. Respir. Crit. Care Med.* 184(7), 842–847 (2011).

29 Travis WD, Costabel U, Hansell DM *et al.* An official american thoracic society/european respiratory society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am. J. Respir. Crit. Care Med.* 188(6), 733–748 (2013).

• **Official ATS/ERS statement on the updated classification of the idiopathic interstitial pneumonias.**

30 Azuma A, Taguchi Y, Ogura T *et al.* Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment. *Respir. Res.* 12, 143 (2011).

31 Cordier JF, Cottin V. Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis. *Eur. Respir. J.* 42(4), 916–923 (2013).

• **Highlights the neglected evidence in idiopathic pulmonary fibrosis with special emphasis on the role of tobacco smoking and earlier diagnosis.**

32 Bradley B, Branley HM, Egan JJ *et al.* Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 63 (Suppl 5), v1–58 (2008).

33 Antoniou KM, Margaritopoulos GA, Siafakas NM. Pharmacological treatment of idiopathic pulmonary fibrosis: from the past to the future. *Eur. Respir. Rev.* 22(129), 281–291 (2013).

34 Xaubet A, Behr J, Bendstrup E *et al.* Review of IPF Diagnosis and Management Recommendations in Europe. *Sarcoidosis Vasc. Diffuse Lung Dis.* (2014) (In press).

35 Schaefer CJ, Ruhrmund DW, Pan L, Seiwert SD, Kossen K. Antifibrotic activities of pirfenidone in animal models. *Eur. Respir. Rev.* 20(120), 85–97 (2011).

•• **Comprehensive review of the antifibrotic properties of pirfenidone in animal studies.**

36 Margolin S, Margolin B, Margolin D. Removal of interstitial pulmonary fibrosis (asbestos-induced) by oral chemotherapy with pirfenidone. *Fed. Proc.* 41, 1550 (1982).

37 Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. *Am. J. Respir. Crit. Care Med.* 159(4 Pt 1), 1061–1069 (1999).

38 Liu H, Drew P, Gaugler AC, Cheng Y, Visner GA. Pirfenidone inhibits lung allograft fibrosis through L-arginine-arginase pathway. *Am. J. Transplant* 5(6), 1256–1263 (2005).

39 Oku H, Shimizu T, Kawabata T *et al.* Antifibrotic action of pirfenidone and prednisolone: different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. *Eur. J. Pharmacol.* 590(1–3), 400–408 (2008).

40 Zhou H, Latham CW, Zander DS, Margolin SB, Visner GA. Pirfenidone inhibits obliterative airway disease in mouse tracheal allografts. *J. Heart Lung Transplant* 24(10), 1577–1585 (2005).

41 Iyer SN, Gurujeyalakshmi G, Giri SN. Effects of pirfenidone on procollagen gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. *J. Pharmacol. Exp. Ther.* 289(1), 211–218 (1999).

42 Kakugawa T, Mukae H, Hayashi T *et al.* Pirfenidone attenuates expression of HSP47 in murine bleomycin-induced pulmonary fibrosis. *Eur. Respir. J.* 24(1), 57–65 (2004).

43 Iyer SN, Hyde DM, Giri SN. Anti-inflammatory effect of pirfenidone in the bleomycin-hamster model of lung inflammation. *Inflammation* 24(5), 477–491 (2000).

44 Nakazato H, Oku H, Yamane S, Tsuruta Y, Suzuki R. A novel anti-fibrotic agent pirfenidone suppresses tumor necrosis factor-alpha at the translational level. *Eur. J. Pharmacol.* 446(1–3), 177–185 (2002).

45 Oku H, Nakazato H, Horikawa T, Tsuruta Y, Suzuki R. Pirfenidone suppresses tumor necrosis factor-alpha, enhances interleukin-10 and protects mice from endotoxic shock. *Eur. J. Pharmacol.* 446(1–3), 167–176 (2002).

46 Carter NJ. Pirfenidone: in idiopathic pulmonary fibrosis. *Drugs* 71(13), 1721–1732 (2011).

47 European Medicines Agency. Esbriet® (pirfenidone) Summary of Product Characteristics (December 2013).

48 Rubino CM, Bhavnani SM, Ambrose PG, Forrest A, Loutit JS. Effect of food and antacids on the pharmacokinetics of pirfenidone in older healthy adults. *Pulm. Pharmacol. Ther.* 22(4), 279–285 (2009).

49 Togami K, Kanehira Y, Tada H. Possible involvement of pirfenidone metabolites in the antifibrotic action of a therapy for idiopathic pulmonary fibrosis. *Biol. Pharm. Bull.* 36(10), 1525–1527 (2013).

50 Azuma A, Nukiwa T, Tsuboi E *et al.* Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 171(9), 1040–1047 (2005).

51 Noble PW, Albera C, Bradford WZ *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 377(9779), 1760–1769 (2011).

•• **Describes the two pivotal Phase III clinical trials of pirfenidone leading to European Medicines Agency approval of pirfenidone for the treatment of mild to moderate idiopathic pulmonary fibrosis in adult patients.**

52 Taniguchi H, Ebina M, Kondoh Y *et al.* Pirfenidone in idiopathic pulmonary fibrosis. *Eur. Respir. J.* 35(4), 821–829 (2010).

53 Du Bois RM, Weycker D, Albera C *et al.* Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am. J. Respir. Crit. Care Med.* 184(12), 1382–1389 (2011).

• **Demonstrates that forced vital capacity is a clinically meaningful outcome for clinical trials in idiopathic pulmonary fibrosis.**

54 Du Bois RM, Weycker D, Albera C *et al.* Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am. J. Respir. Crit. Care Med.* 183(9), 1231–1237 (2011).

55 Ishii H, Kushima H, Komiya K, Mizunoe S, Kadota J. Pharmacological therapy does not contribute to survival in idiopathic pulmonary fibrosis. *Respiration* 86(1), 86–87 (2013).

56 Spagnolo P, Del Giovane C, Luppi F *et al.* Non-steroid agents for idiopathic pulmonary fibrosis. *Cochrane Database Syst. Rev.* (9), CD003134 (2010).

57 Costabel U, Albera C, Bradford WZ *et al.* Analysis of lung function and survival in RECAP: an open-label extension study of pirfenidone in patients with idiopathic pulmonary fibrosis [Abstract]. *Eur. Respir. J.* 40 (Suppl 56), 511s (2012).

58 Iwasawa T, Ogura T, Sakai F *et al.* CT analysis of the effect of pirfenidone in patients with idiopathic pulmonary fibrosis. *Eur. J. Radiol.* 83(1), 32–38 (2014).

59 Sakamoto S, Itoh T, Muramatsu Y *et al.* Efficacy of Pirfenidone in Patients with Advanced-stage Idiopathic Pulmonary Fibrosis. *Intern. Med.* 52(22), 2495–2501 (2013).

60 European Medicines Agency. Pirfenidone CHMP assessment report (2010). www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002154/WC500103073.pdf

61 Jiang C, Huang H, Liu J, Wang Y, Lu Z, Xu Z. Adverse events of pirfenidone for the treatment of pulmonary fibrosis: a meta-analysis of randomized controlled trials. *PLoS One* 7(10), e47024 (2012).

62 Valeyre D, Albera C, Bradford WZ *et al.* Comprehensive assessment of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis. *Respirology* (2014) (In Press).

63 Itoh T, Koyabu K, Morimoto A *et al.* Ameliorative effects of mosapride or Rikkunshi-to on the suppression of gastrointestinal motility by pirfenidone in rats. *Jpn. Pharmacol. Ther.* 40(5), 405–411 (2012).

64 Seto Y, Inoue R, Kato M, Yamada S, Onoue S. Photosafety assessments on pirfenidone: photochemical, photobiological, and pharmacokinetic characterization. *J. Photochem. Photobiol. B* 120, 44–51 (2013).

65 Pharmaceuticals and Medical Devices Agency Japan. Pirfenidone report (2007). www.pmda.go.jp/english/service/pdf/drugs/pirespa_oct2008_e.pdf

66 Chaudhuri N, Duck A, Frank R, Holme J, Leonard C. Real-world experiences: Pirfenidone is well tolerated in patients with idiopathic pulmonary fibrosis. *Respir. Med.* 108(1), 224–226 (2013).

67 Costabel U, Bendstrup E, Cottin V *et al.* Pirfenidone in idiopathic pulmonary fibrosis: expert panel discussion on the management of drug-related adverse events. *Adv Ther* (2014) (In press).

68 InterMune. Data on file.

69 Bonella F, Wessendorf TE, Costabel U. [Clinical experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis]. *Dtsch. Med. Wochenschr.* 138(11), 518–523 (2013).

70 Bonella F, Wessendorf TE, Costabel U. Clinical experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis. P3808. Presented at: *European Respiratory Society Annual Congress*. Barcelona, Spain, 7–11 September 2013.

71 Oltmanns U, Kahn H, Wenz H *et al.* Pirfenidone in idiopathic pulmonary fibrosis: Real-life experience from a German tertiary referral centre for interstitial lung diseases. P2335. Presented at: *European Respiratory Society Annual Congress*. Barcelona, Spain, 7–11 September 2013.

72 Okuda R, Hagiwara E, Baba T, Kitamura H, Kato T, Ogura T. Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice. *Respir. Med.* 107(9), 1431–1437 (2013).

73 Arai T, Inoue Y, Sasaki Y *et al.* Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis. *Respiratory Investigation* doi:10.1016/j.resinv.2013.09.002 (2013) (Epub ahead of print).

74 Ravaglia C, Gurioli C, Romagnoli M *et al.* Pirfenidone treatment in idiopathic pulmonary fibrosis: an Italian case series. P3370. Presented at: *European Respiratory Society Annual Congress*. Barcelona, Spain, 7–11 September 2013.

75 Nieto Barbero MA, Valenzuela C, Rivera Ortega P *et al.* Pirfenidone in idiopathic pulmonary fibrosis (IPF): Early Spanish experience with the European Named patient program (NPP). P2361. Presented at: *European Respiratory Society Annual Congress*. Barcelona, Spain, 7–11 September 2013.

76 Wijsenbeek MS, Van Beek FT, Geel AL *et al.* Pirfenidone in daily clinical use in patients with idiopathic pulmonary fibrosis in the Netherlands. A4340. Presented at: *American Thoracic Society International Conference*. Philadelphia, PA, USA, 17–22 May 2013.

77 Russell AM, Vancheri C, Maronati M, Giot C. A qualitative European survey of patients perceptions of current management of idiopathic pulmonary fibrosis. Presented at*: British Thoracic Society Winter Meeting*. London, UK, 4–6 December 2013.

78 Trivedi R, Redente EF, Thakur A, Riches DW, Kompella UB. Local delivery of biodegradable pirfenidone nanoparticles ameliorates bleomycin-induced pulmonary fibrosis in mice. *Nanotechnology* 23(50), 505101 (2012).

79 Onoue S, Seto Y, Kato M, Aoki Y, Kojo Y, Yamada S. Inhalable powder formulation of pirfenidone with reduced phototoxic risk for treatment of pulmonary fibrosis. *Pharm Res* 30(6), 1586–1596 (2013).

80 Allen JT, Spiteri MA. Growth factors in idiopathic pulmonary fibrosis: relative roles. *Respir Res* 3, 13 (2002).

81 Richeldi L, Costabel U, Selman M *et al.* Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N. Engl. J. Med.* 365(12), 1079–1087 (2011).

82 Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N. Engl. J. Med.* 366(21), 1968–1977 (2012).

83 Maher TM, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? *Eur. Respir. J.* 30(5), 835–839 (2007).

84 Lota HK, Wells AU. The evolving pharmacotherapy of pulmonary fibrosis. *Expert Opin Pharmacother* 14(1), 79–89 (2013).