

## LONG-TERM MANAGEMENT OF IPF WITH PIRFENIDONE – A CLINICAL CASE STUDY WITH 5 YEARS FOLLOW-UP

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**ABSTRACT.** Idiopathic pulmonary fibrosis (IPF) is a progressively fibrotic interstitial lung disease that is associated with a median survival of 2–5 years from initial diagnosis. To date, the search for an effective treatment has involved numerous clinical trials of investigational agents but without significant success. Nevertheless, research over the past 10 years has provided us with a wealth of information on its histopathology, diagnostic work-up, and a greater understanding of its pathophysiology. Specifically, IPF is no longer thought to be a predominantly pro-inflammatory disorder. Rather, the fibrosis in IPF is increasingly understood to be the result of a fibroproliferative and aberrant wound healing cascade. The development of therapeutic targets has therefore shifted in accordance with this paradigm change. Emerging clinical data from recently published and ongoing trials investigating new potential pharmacological agents should be considered in the routine clinical management of these patients. Based upon encouraging results from randomised-controlled trials showing a positive effect in slowing decline in pulmonary function and reducing disease progression, pirfenidone was approved in 2011 as the first treatment in patients with IPF. This case study describes the clinical course of a patient enrolled into the Phase III and open-label extension studies of pirfenidone. (*Sarcoidosis Vasc Diffuse Lung Dis* 2013; 30 Suppl 1: 52-62)

**KEY WORDS:** idiopathic pulmonary fibrosis, drug therapy, pirfenidone, CAPACITY, RECAP

### INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is one of the idiopathic interstitial pneumonias with the worst prognoses, with approximately half of patients dying within 3–5 years (1). The aetiology of IPF is still unknown and its pathogenesis is poorly understood. The management of patients with IPF is based largely on the recommendations of scientific societies, such as the American Thoracic Society (ATS) and the European Respiratory Society (ERS) (1). The recently updated 2011 joint statement of the

ATS, the ERS, the Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT) provided an assessment of the currently available evidence regarding treatments for IPF and includes systematic reviews of each of the therapeutic agents used in published clinical trials (1). These recommendations are intended to empower clinicians to interpret the available evidence in the context of individual patient values and preferences, and to make appropriate decisions regarding all aspects of disease management, tailored to the patient with typical IPF.

Treatment decisions for patients with IPF should be based primarily on the findings of evidence derived from placebo-controlled randomised controlled trials (RCT). Since 2004 there has been an exponential increase in the number of clinical tri-

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als investigating the treatment of IPF (Figure 1) (2). Anti-oxidant, anti-coagulant, and anti-inflammatory drugs such as corticosteroids and some immunosuppressants have been used to treat IPF, although they have not been objectively proven to be effective by large-scale RCTs (3–12). Thus, despite progress in pathophysiology understanding, better diagnostic definition, and substantial investments by pharmaceutical companies, the management of IPF patients has remained a major medical challenge (13–15).

### NOVEL TREATMENTS IN IPF

To date, the search for effective treatment for IPF has involved numerous clinical trials of investigational agents but without significant success. Nevertheless, research over the past 10 years has provided us with a wealth of information on its histopathology, diagnostic work-up, and a greater understanding of its pathophysiology. Specifically,

IPF is no longer thought to be a predominantly pro-inflammatory disorder. Rather, the fibrosis in IPF is increasingly understood to be the result of a fibro-proliferative and aberrant wound healing cascade. The development of therapeutic targets has therefore shifted in accordance with this paradigm change and there are numerous ongoing trials investigating potential therapeutic agents acting on various targets with a notable shift from corticosteroids and/or immunosuppressants to anti-fibrotic agents (Table 1) (16–29).

Pirfenidone (Esbriet®) is the first anti-fibrotic treatment to be approved for clinical use for the treatment of patients with mild-to-moderate IPF. Pirfenidone acts as an anti-fibrotic agent by directly altering the expression, synthesis, and possibly accumulation of collagen, and inhibiting the recruitment, proliferation and possibly expression of the extracellular matrix-producing cells (30). To date, four placebo-controlled, RCTs (one Phase II and three Phase III studies) have evaluated the treatment of

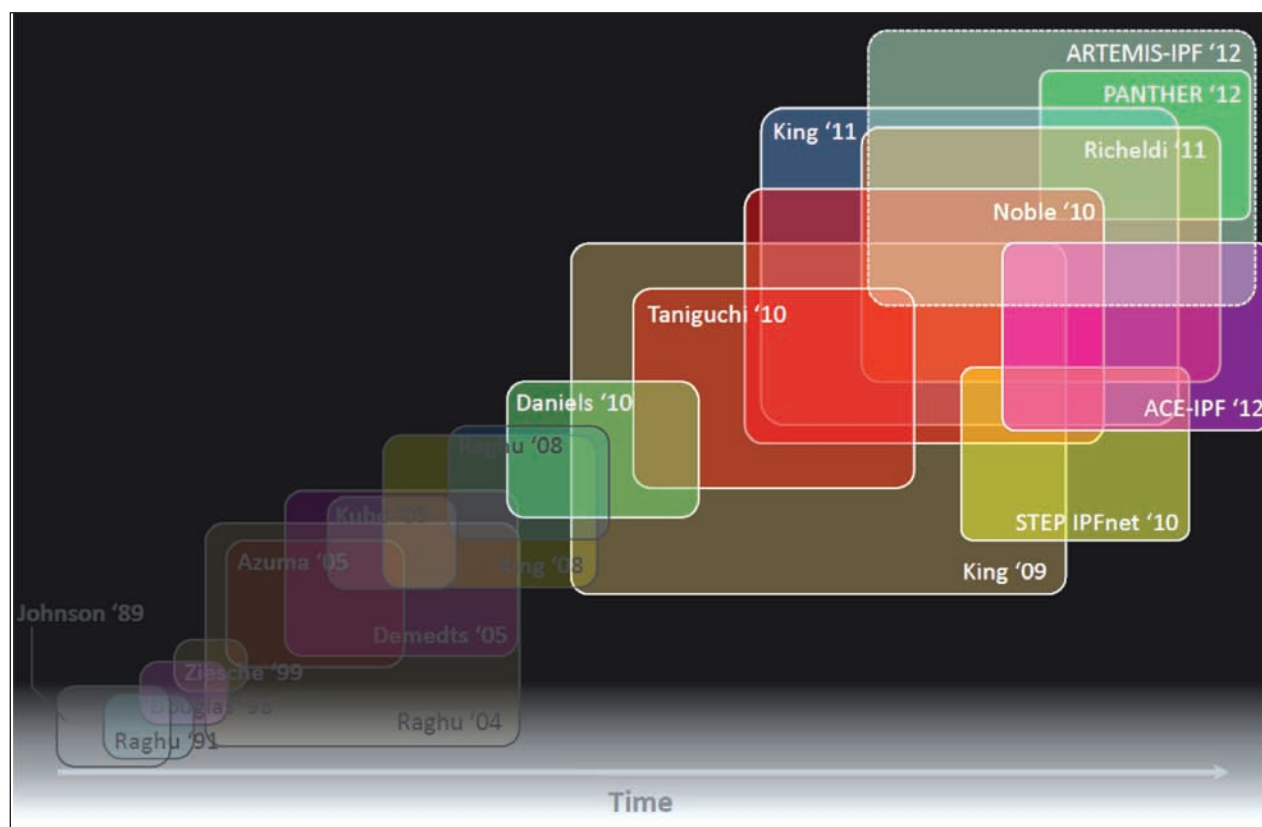


Fig. 1. Randomised controlled trials in IPF. Size of box represents sample size for each trial

**Table 1.** Overview of recent and ongoing clinical trials in IPF (16)

Agent/treatment	Potential mechanism of action	Select clinical trial or retrospective series	Clinical trials registry number	Study design where appropriate	End points and duration of trial where appropriate / available	Outcome / comments
Azathioprine + Prednisolone with or without N-acetylcysteine (NAC)	Antioxidant, immunosuppressant-inflammation	IFIGENIA trial Demedts et al. (2005)	NCT00639496	Prospective, double-blinded, randomized placebo – controlled trial; NAC + azathioprine + prednisolone (n=92) vs. placebo + azathioprine + prednisolone (n=90)	Primary end points: absolute $\Delta$ FVC and DLco at 12 months	Trial completed; reduction in FVC and DLco decline over 1 year in NAC arm, though no change in mortality
N-acetylcysteine (NAC) with or without Azathioprine + Prednisolone	Antioxidant, immunosuppressant, anti-inflammatory	Panther-IPF trial NHLBI, USA Raghu et al. (2012)	NCT00650091	Prospective, double-blinded, randomized placebo – controlled trial; currently recruiting patients, planned enrollment n=390	Primary end point: $\Delta$ FVC at 60 weeks	Increased mortality observed in the triple therapy arm. Triple treatment arm stopped for safety. Subjects on NAC or placebo alone continue to be followed
Pirfenidone	Antifibrotic inhibitor of TGF $\beta$ , anti-inflammatory, antioxidant	Taniguchi et al. (2010)	None available	Prospective, double-blinded, randomized placebo – controlled trial; high dose pirfenidone (n=108) vs. low dose pirfenidone (n=55) vs. placebo (n=104)	Primary end point: $\Delta$ FVC at 52 weeks	Significant reduction in FVC decline in high dose treatment arm. However, change in end point during trial, handling of missing data and absence of patient reported outcome means it is difficult to draw firm conclusions at this time
Pirfenidone	As above	CAPACITY I trial (Intermune, USA) Noble et al. (2011)	NCT00287729	Prospective, double-blinded, randomized placebo – controlled trial; high dose pirfenidone (n=171) vs. placebo (n=173)	Primary end point: $\Delta$ FVC at 72 weeks	Trial completed; no significant difference in FVC decline between treatment groups
Pirfenidone	As above	CAPACITY 2 trial (InterMune, USA) Noble et al. (2011)	NCT00287716	Prospective, double-blinded, randomized placebo – controlled trial; high dose pirfenidone (n=174) vs. low dose pirfenidone (n=87) vs. placebo (n=174)	Primary end point: $\Delta$ FVC at 72 weeks	Trial completed; significant reduction in FVC decline in pirfenidone groups

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**Table 1.** Overview of recent and ongoing clinical trials in IPF (16)

Pirfenidone	As above	ASCEND trial (InterMune, USA)	NCT01366209	Prospective, double-blinded, randomized placebo – controlled trial; high dose pirfenidone vs. placebo; planned enrollment n=500	Primary end point: $\Delta$ 96FVC at 52 weeks	Trial ongoing; results awaited
GCI008	Anti-TGF $\beta$ 1, 2, and 3 antibody	Genzyme and Cambridge Antibody Technology, UK	NCT00125385	Non-randomized, open label, single group assignment Phase I study (n=25)	Primary end points: safety and tolerability Secondary end points: potential clinical outcomes up to 3 years	Trial completed; results awaited
STX-100	Anti- $\alpha$ v $\beta$ 6 integrin	Stromedix, USA	NCT01371305	Phase I studies completed (Stromedix) – awarded orphan drug status (USA) and a Phase II study is ongoing; planned enrollment n=35	Primary end points: safety over 24 weeks	Phase I Trial completed, results awaited; Phase II Trial ongoing
FG-3019	Connective tissue growth factor inhibitor	Fibrogen, USA	NCT00074698	Open-label Phase I study completed (n=21) – awarded orphan drug status (USA); an open-label Phase II study is ongoing (n=84)	Phase II trial primary end point: safety at 45 weeks Secondary end points: effect on extent of pulmonary fibrosis, pulmonary function and dyspnea	Phase I trial completed; FG-3019 is safe and well-tolerated. Future trials will assess therapeutic potential Phase II Trial ongoing
Octeotide	Somatostatin analogue	Institut National de la Santé Et de la Recherche Médicale, France	NCT00463983	Non-randomized open label single interventional study with octeotide (n=25)	Monitoring of FVC; DLco; HRCT fibrosis score; 6MWD over 48 weeks	Trial completed, trend of decline in FVC and DICO was lower in subjects treated with octeotide compared to historical, previously published data from other trials
CNTO 888	Anti-CCL2 antibody	Centocor, USA	NCT00786201	Prospective double-blinded, randomized placebo-controlled Phase II trial; CNTO 888 $\pm$ usual therapy vs. placebo $\pm$ usual therapy; currently recruiting patients, planned total n=120	Primary end points: safety and performance at lung function tests.	Trial completed; results awaited

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QAX576	Anti-IL-13 antibody; IL-13 stimulates collagen deposition and myofibroblast differentiation	Novartis, Switzerland	NCT00532233	Open label Phase II study (n=50)	Primary end point: IL-13 serum levels Secondary end point: change in designated serum biomarkers over time with treatment for 4 weeks	Trial completed; results awaited
Tralokunimab	Anti-IL-13 antibody; IL-13 stimulates collagen deposition and myofibroblast differentiation	MedImmune LLC.	NCT01629667	Prospective double-blinded, randomized placebo-controlled Phase II study; high dose tralokinumab vs. low dose tralokinumab vs. placebo, planned enrollment n=186	Primary end point: change from baseline in FVC at week 72 Secondary end point: safety	Trial ongoing
SARI56597	Bispecific Anti-IL-13 and IL-4 antibody; IL-13 stimulates collagen deposition and myofibroblast differentiation; IL-4 promotes fibroproliferation	Sanofi-Aventis	NCT01529853	Prospective double-blinded, randomized placebo-controlled Phase II study; SARI56597 vs. placebo, planned enrollment n=24	Primary end point: safety and tolerability over 6 months Secondary end point: change in FVC, DICO and dyspnea score from baseline	Trial ongoing
Thalidomide	Anti-angiogenic immunomodulatory anti-inflammatory inhibitor of TGF $\beta$ -I signaling and VEGF expression	Investigator led- John Hopkins University, USA	NCT00162760	Non-randomized open label single interventional study designed for patients who have failed or are unsuitable for immunosuppressive therapy; planned enrollment n=19	Primary end point: safety Secondary end points: $\Delta$ lung function over 1 year	Trial completed; results awaited
GS6624	Anti-LOXL2 antibody; this enzyme generates crosslinks fibrillar collagen to generate the scaffold on which fibroblasts grow	Gilead Sciences	NCT01362231	Randomized, double-blind, dose escalation study of GS-6624 vs. placebo; planned enrollment n=48	Primary end point: safety and tolerability	Phase I trial completed; Phase II trial planned
BIBF I 120	Angiokinase inhibitor targeting proliferative growth factors in fibroblasts (FGFR, PDGFR, VEGFR)	TOMORROW trial Boehringer Ingelheim Pharmaceuticals, UK	NCT00514683	Prospective, double-blinded, randomized placebo-controlled Phase II study; BIBFI 120 vs. placebo; total (n=400) recruitment complete	Primary end point: $\Delta$ FVC over 1 year Secondary end point: dyspnea score, survival	Trial completed; results awaited

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**Table 1.** Overview of recent and ongoing clinical trials in IPF (16)

BIBF I 120	As above	INPULSISTM-1 and INPULSISTM-2 trials Boehringer Ingelheim Pharmaceutical, UK	NCT01335464 and NCT01335477	Prospective, double-blinded, randomized placebo-controlled Phase III studies; BIBF I 120 vs. placebo; planned enrollment n=515 and n=551, respectively	Primary end point: $\Delta$ FVC over 52 weeks	Trials ongoing
Minocycline	Broad spectrum tetracycline with anti-inflammatory and anti-angiogenic properties	Investigator-led trial- University of California, USA	NCT00203697	Prospective, double-blinded, randomized placebo-controlled trial; patient numbers not disclosed	Primary end points: safety and efficacy	Trial status unknown; results awaited
Tetrathiomolybdate	Angiogenic	Investigator-led trial-University of Michigan, USA	NCT00189176	Non-randomized, open label, uncontrolled, single group assignment Phase I/II (n=20)	Primary end point: safety Secondary end points: $\Delta$ lung function tests	Trial completed; results awaited
Doxycycline	MMP inhibitor; some MMPs drive cellular apoptosis, migration, proliferation, and angiogenesis	Indian Institute of Chemical Biology	None available	Non-randomized, open label, uncontrolled, single group assignment (n=6)	Primary end point: inhibition of MMP activity in the BALF at 6 months Secondary end points: $\Delta$ FVC, 6MWD, and dyspnea score	Trial completed; a non-statistical trend toward improved 6MWD and FVC
Losartan	Angiotensin II inhibitor	National Cancer Institute, USA	NCT00879879	Open label interventional study; recruiting patients; planned enrollment n=25	Primary end point: FVC response at 1 year	Trial status unknown; results awaited
Carbon monoxide	Anti-proliferative diatomic gas, inhibitor of fibroblast ECM deposition	Birgham and Women's Hospital, USA	NCT01214187	Prospective, double-blinded randomized placebo-controlled trial; carbon monoxide vs. placebo, currently recruiting, planned enrollment n=60	Primary end point: $\Delta$ serum baseline MMP7 level at 3 months	Trial ongoing
Adjunctive treatment of GER with PPI or H2 receptor blockers	Gastroesophageal therapy and/or prophylaxis	Lee et al. (2011) Raghu et al. (2006)	None available	Retrospective case series; PPI or H2 blockers vs. no GER therapy; (n=204)	Primary end point: survival from time of IPF diagnosis	Decreased HRCT fibrosis score (14 vs. 1996) and improved survival (HR=0.47) in the GER therapy group

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Mesenchymal stem cells	Potential alveolar re-epithelialization	The Prince Charles Hospital, Australia	NCT01385644	Prospective, open-label trial; low-dose mesenchymal stem cells (MSC) vs high dose MSC; planned enrollment n=8	Primary end point: safety 6 months post treatment	Trial ongoing
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6MWD, 6 min walk test distance; A-a, alveolar:arterial ANZCTR, Australian New Zealand clinical trials registry; BALF, bronchoalveolar lavage fluid; CCL-2, Chemokine (C-C motif) ligand 2; cGMP, cyclic guanosine monophosphate; CRP, clinical-radiographic-physiological; DLco, carbon monoxide dilution; FGFR, fibroblast growth factor receptor; FVC, forced vital capacity; H2, histamine H2 receptor blocker; HRCT, high resolution computer tomography; IFN- $\gamma$ , interferon-gamma; IL-13, interleukin 13; IL-4, interleukin 4; LOXL-2, lysyl oxidase-like enzyme 2; MMP, matrix metalloproteinase; NCT, clinicaltrials.gov identifier; PDGFR, platelet-derived growth factor receptor; PPI, proton pump inhibitor; pred, predicted QoL, quality of life; TGF $\beta$ , transforming growth factor-beta; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Reprinted from the *Journal of Thoracic Disease* with permission from Pioneer Bioscience Publishing Company (16).

IPF patients with pirfenidone. The Phase III CAPACITY (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) study programme consisted of two concurrent multinational RCTs (Studies 004 and 006) (31). While the primary endpoint (change in % predicted FVC from baseline to Week 72) was met in the 004 study (n=435; p=0.001), it was not met in the 006 study (n=344; p=0.501). However, a significant pirfenidone treatment effect (estimated by differences in treatment group means and categorical change in FVC) was noted all time points from Week 12 until Week 48 in the 006 study.

The difference in FVC outcomes in the two studies might be partly attributable to a lower than expected rate of FVC decline in the placebo arm of study 006 after one year, while the magnitude of decline over time was similar in the two pirfenidone groups. In the primary analyses of both studies, the magnitude of treatment effect was similar at all assessment time points over one year. Indeed, pooled data from both studies provide compelling evidence that pirfenidone reduces decline in lung function and disease progression (31).

Pirfenidone appears to be generally well tolerated. The most common side effects in clinical trials were gastrointestinal upset, fatigue, nausea, anorexia, and dermatological problems, including photosensitivity.

An open-label extension phase of the CAPACITY studies (RECAP) was designed to assess the safety of pirfenidone beyond the duration of the Phase III studies (32). This case study describes the clinical course of a patient enrolled originally into the CAPACITY 004 Study and then into the RECAP Study.

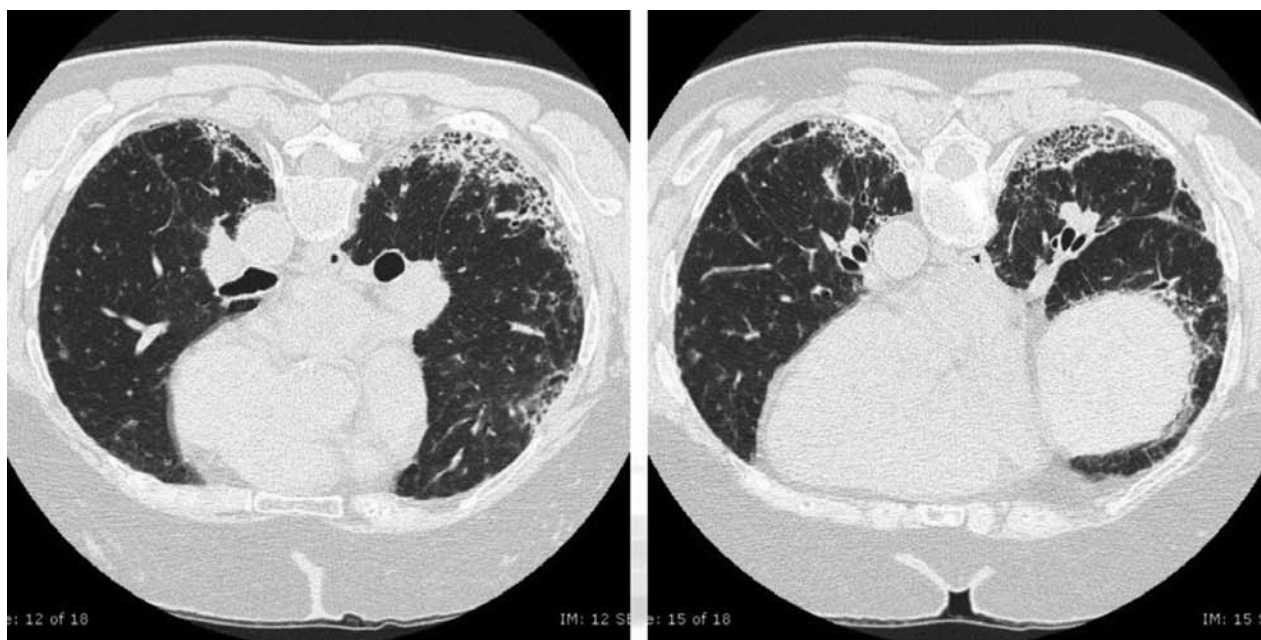
## CASE REPORT

### Presentation

A 77-year-old, non-smoking, Italian female with an allergy to acetylsalicylic acid and who was affected by anxious-depressive syndrome presented with dry cough in June 2006. This was followed by the onset of exertional dyspnoea in October 2006. Because of worsening of her dyspnoea, the patient underwent a chest X-ray that showed a consolidation (compatible with the diagnosis of bronchopneumonia), which was effectively treated with antibiotics and steroids. A further X-ray showed clearing of the area of consolidation, but cough and breathlessness persisted.

### Diagnosis

On 28 February 2007 the patient underwent a high-resolution computed tomography (HRCT) scan of the chest, which showed evidence of diffuse interstitial lung disease in basal lung regions, characterised by peripheral reticular opacities, traction bronchiectasis, honeycomb lung destruction, and irregular areas of consolidation with no ground-glass opacities, consistent with usual interstitial pneumonia (Figure 2) (33). In order to exclude other known causes of pulmonary fibrosis, a bronchoscopy with bronchoalveolar lavage was performed but did not provide evidence for any alternative diagnoses. Based on the patient's clinical history, other secondary causes of interstitial lung disease (such as connective



**Fig. 2.** HRCT scans in February 2007 showing predominantly bibasal and peripheral reticular opacities, traction bronchiectasis, and honeycomb lung destruction. (Figure provided with courtesy of Dr. Sgalla)

tissue diseases or drug toxicity) were also excluded and a diagnosis of IPF was established.

### *Treatment*

In May 2007, the patient agreed to enrol into the CAPACITY 004 clinical trial and began treatment with pirfenidone (2403 mg/day administered in three equally divided doses tid). During the study, the patient underwent several follow-up visits in which pulmonary function tests with diffusing lung capacity for carbon monoxide (DLco) were performed, together with blood tests, a 6-min walking test, and electrocardiogram. The University of California, San Diego Shortness of Breath questionnaire, the St George's Respiratory Questionnaire and the World Health Organization Quality of Life-100 questionnaire were used at the beginning of the trial to gain information about dyspnoea and quality of life.

### *Outcomes*

After 6 weeks of treatment in June 2007, the patient reported a reduction in cough symptoms and decreased appetite and a further reduction in cough and subjective improvement in respiratory symp-

toms up to September 2007. In October 2007, the patient was seen in an unscheduled visit due to the onset of general malaise, hypotension, dizziness, and anorexia, with altered perception of smell and taste. This was considered a likely consequence of intolerance to the highest dosage of the pirfenidone; therefore, the dosage was reduced to 1602 mg/day. At Week 24 of the study, despite sporadic but treatable episodes of tracheitis, pharyngitis, bronchitis, and labyrinthitis, the patient's clinical condition improved. At the end of the CAPACITY Study, the patient's clinical conditions were stable.

In October 2008, the patient enrolled in the RECAP extension study and completed quarterly follow-up visits and assessments of pulmonary function and blood tests up until March 2012, at which time the patient became eligible to receive pirfenidone through the European Named Patient Program. During nearly four years of follow-up the patient did not report any other side effect related to pirfenidone, or any acute exacerbations of IPF. Additional sporadic episodes of pharyngitis and bronchitis occurred but these were all effectively treated with antibiotics. After regulatory approval of pirfenidone in Europe, given the persistent stability in clinical condition and upon approval by the local



ethics committee, the patient continued to receive pirfenidone under the European Named Patient Program. During more than five years of pirfenidone treatment, we observed long-term stability in FVC as compared to baseline, with a marginal improvement between 2008 and 2010 (Figure 3). A significant decline in carbon monoxide diffusing capacity (DLco) was evident since 2011.

In February 2013 a new HRCT of the chest was performed, highlighting a progression of the fibrotic process with a larger extension of the honeycomb changes in the right upper lobe (Figure 4). At the last follow-up visit in March 2013 the patient referred worsening of cough and dyspnoea on exertion in the last months; pulmonary function tests showed further worsening of DLco. At this time the 6-

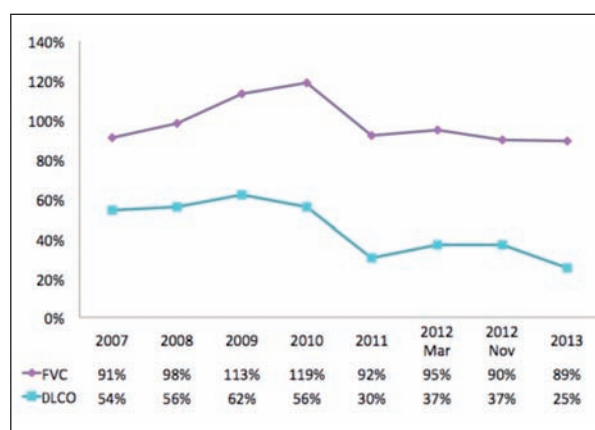


Fig. 3. Pulmonary function data measured annually.

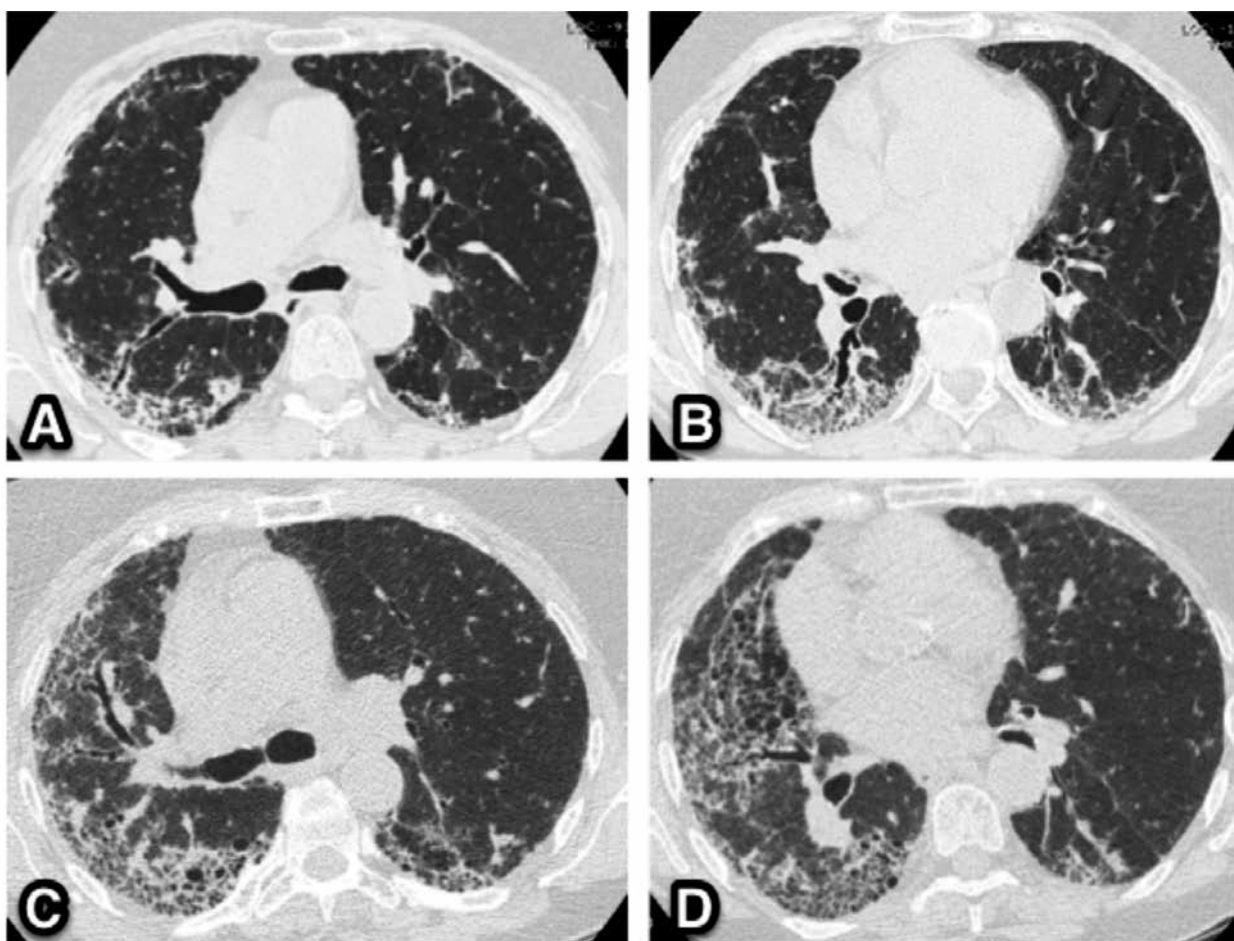


Fig. 4. Chest HRCT scans showing progression of fibrosis in the upper and medium right lobe from 2008 (images A and B) to 2013 (images C and D).

minute walking test revealed a significant oxygen desaturation, and long-term supplemental oxygen therapy during exertion was then prescribed.

## DISCUSSION

The outcomes of treatment with pirfenidone in this patient were generally better than those reported in the CAPACITY trials. The worsening in symptoms and the slight impairment in pulmonary function occurred only after five years of substantial stability, as the result of the slow but progressive extension of the fibrotic process in the lungs (as demonstrated by the last chest HRCT), supporting the evidence that treatment with pirfenidone might result in a relevant diminution of the functional decline. Although the functional stability observed in this particular patient may be due to the natural history of the disease and a favourable course of the fibrotic process, a drug-related benefit is supported by the patient's rapid and sustained improvement in respiratory symptoms after starting treatment with pirfenidone. These benefits persisted for a long time even after dosage reduction. The patient did experience some of the most frequent adverse events reported for pirfenidone in the CAPACITY trials, such as general malaise, anorexia, and gastrointestinal symptoms. However, these dissipated after dose reduction, confirming the overall favourable tolerability profile of pirfenidone.

It is clear that treatment decisions and the clinical management of patients with IPF should be based primarily on the collective findings from RCTs. Based on the available evidence in 2010, the key message from the 2011 guidelines on diagnosis and management of IPF developed by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) is that no pharmacological treatments are strongly recommended for patients with IPF. This is due predominantly to the insufficient or inadequate quality of data regarding the risks and benefits supporting their use (1). However, discrepancies between the decisions of the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the 2011 international guideline committee demonstrate that there are different ways to interpret

data from RCTs. While the FDA refused approval of pirfenidone based on the two CAPACITY Studies, the drug was approved for use in Japan in 2008 and in India in 2010, and in Europe in 2011 by the EMA for patients with mild-to-moderate IPF. However, the ATS/ERS/JRS/ALAT guideline committee gave a 'Weak No' recommendation for pirfenidone, with high value placed on costs and side effects and low value on the possible small reduction in pulmonary decline (1). It must be noted, however, that the majority of committee members (16/31) abstained from voting on pirfenidone as most were involved in the CAPACITY trials. In addition, the guidelines were devised before full publication of the CAPACITY study data. Further clinical trials of pirfenidone are ongoing or planned, including ASCEND (Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis [IPF]), a Phase III trial of pirfenidone aiming to confirm a clinically meaningful effect on FVC (clinicaltrials.gov identifier NCT01366209).

As a consequence, in countries in which pirfenidone is approved, eligible patients are considered for this new therapeutic option. A recent European online survey including responses from 66 respiratory specialists attending the pan-European meeting showed that 42% chose pirfenidone as first-line treatment for newly diagnosed IPF, representing a rapid increase from 11% of specialists responding to a similar survey at the first AIR meeting in 2011 (34). In the latest survey only 4% of specialists said they would use triple therapy with prednisone, azathioprine and N-acetylcysteine as first-line IPF therapy. This was a major reduction from 26% in the previous survey in 2011.

There is an increasing awareness of comorbid conditions frequently associated with IPF, including emphysema, cardiovascular disease, thromboembolic disease, and obstructive sleep apnoea. Recent retrospective data suggest that 21 to 33% of patients with IPF may have co-existing emphysema. The association of emphysema with IPF has been termed the combined pulmonary fibrosis and emphysema (CPFE) syndrome to account for the characteristic clinical, functional, imaging, and outcome features. Various examples of the practical use of pirfenidone in these and other individual cases of IPF seen commonly in clinical practice are described in the following section of this supplement.

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## DISCLOSURES:

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