Real world experience of response to pirfenidone in patients with idiopathic pulmonary fibrosis: a two centre retrospective study

James A. Eaden[1,2], Christopher M. Barber[2], Stephen A. Renshaw[1,2], Nazia Chaudhuri[3], Stephen M. Bianchi[2]

[1] Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom; [2] Respiratory Medicine Department, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; [3] Interstitial Lung Disease Unit, University of Manchester NHS Foundation Trust, Manchester, United Kingdom

Abstract. *Introduction:* Pirfenidone has been shown to reduce the decline in forced vital capacity (FVC) compared to placebo in patients with idiopathic pulmonary fibrosis (IPF). Previous studies have suggested that patients with a more rapid decline in FVC during the period before starting pirfenidone experience the greatest benefit from treatment. The purpose of this retrospective observational study was to investigate the response to pirfenidone in IPF patients, comparing two groups stratified by the annual rate of decline in FVC % predicted prior to treatment. *Methods:* Using the rate of decline in FVC % predicted in the 12 months prior to pirfenidone, patients were stratified into slow (<5%) or rapid (≥5%) decliner groups. Comparisons in the lung function response to pirfenidone in these two groups were performed. *Results:* Pirfenidone resulted in no statistically significant reduction in the median annual rate of decline in FVC or FVC % predicted. In the rapid decliners, pirfenidone significantly reduced the median (IQR) annual rate of decline in FVC % predicted (-8.7 (-14.2 − -7.0) %/yr vs 2.0 (-7.1 − 6.0) %/yr; n=17; p<0.01). In the slow decliners, pirfenidone did not reduce the median (IQR) annual rate of decline in FVC % predicted (-1.3 (-3.2 − 1.3) %/yr vs -5.0 (-8.3 − -0.35) %/yr; n=17; p=0.028). *Conclusions:* We demonstrate the greater net effect of pirfenidone in IPF patients declining rapidly. We suggest that using an annual rate of decline in FVC of <5% and ≥5% may be useful in counselling patients with regard to pirfenidone treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 218–224)*

Key words: idiopathic pulmonary fibrosis, pirfenidone, forced vital capacity, efficacy, treatment

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible interstitial lung disease (ILD) of unknown aetiology. Four large, multicentre randomised controlled trials (RCTs) have shown that pirfenidone

is able to reduce the progression of IPF compared to placebo, as well as being safe and well tolerated (1-3). In 2013, the National Institute for Health and Care Excellence (NICE) in the United Kingdom approved the use of pirfenidone in IPF patients with a forced vital capacity (FVC) of 50-80% predicted (4). Nintedanib, a tyrosine kinase inhibitor, was approved by NICE for the treatment of IPF in 2016 (5).

Data from an interim analysis of a long-term, open-label extension study (RECAP) involving 603 patients who took part in the CAPACITY trials, showed that 69% of patients receiving pirfenidone were alive at week 228 (4.4 years) and that after five

years, approximately half of the patients who were initially randomised to pirfenidone were still taking it (6). A pre-specified pooled analysis of 1,247 patients from the CAPACITY trials and the ASCEND study found that compared to placebo, pirfenidone reduced the risk of death at one year by 48% (7). It also demonstrated a consistent treatment effect across sub-populations, including those stratified by age and severity of disease.

RCTs of pirfenidone in IPF tend to poorly reflect patients treated in usual clinical practice. Study patients have less comorbidities, a specific severity of disease defined only by FVC and an age limit of less than 80 years of age. Open label studies and both prospective and retrospective reports of outcomes from usual clinical practice offer insights beyond those gleaned from RCTs.

A number of observational studies confirming the safety and efficacy of pirfenidone in patients with IPF in the real world have been published (8-21). Three of these have suggested that patients with a more rapid decline in FVC during the period before starting pirfenidone experience the greatest benefit from treatment determined by a significant improvement in FVC decline over a six month (10, 21) and a 12-month follow-up period (13).

In this retrospective observational study, we investigated the response to pirfenidone in patients with IPF, comparing two groups stratified by the annual rate of decline in FVC % predicted prior to treatment.

Methods

The article has been approved by Ethics Committee. We performed a retrospective observational study of IPF patients treated with pirfenidone in two tertiary referral centres for ILD in the North of England. The clinical records of 68 IPF patients commencing pirfenidone between June 2013 and March 2015 at the Northern General Hospital, Sheffield were reviewed. All patients fulfilled the NICE criteria of a FVC 50-80% predicted. The clinical records of 351 patients with IPF commencing pirfenidone between September 2011 and February 2016 at the Manchester University NHS Foundation Trust, Wythenshawe Hospital, Manchester were reviewed. These patients were either involved in the manu-

facturer-funded Named Patient Programme (NPP) for pirfenidone between September 2011 and April 2013 (n=48) or were treated after the approval of pirfenidone by NICE in April 2013 (n=303). Those patients involved in the NPP had a FVC of at least 50% predicted and/or diffusing capacity of the lungs for carbon monoxide (D_{LCO}) of at least 35% predicted. The patients who were treated following NICE approval had a FVC 50-80% predicted. All patients had a multidisciplinary team (MDT) diagnosis of probable or definite IPF as per the ATS/ERS consensus statement of 2011 (22).

Pirfenidone was prescribed as per manufacturer recommendations and was titrated to a dose of three 267mg capsules three times daily (total 2403mg/day), as tolerated. At each clinical review, details of any adverse event and the subsequent management strategy were documented. Dose modifications due to adverse events were implemented on an individual patient basis, according to the patient's response. Data regarding the number and type of adverse events were collected, including the number of patients who discontinued pirfenidone or had a change in treatment dose. Full blood count, urea and electrolytes and liver function tests were taken prior to commencing pirfenidone, and then monitored at each clinical review. Baseline demography collected included age, sex, body mass index (BMI), smoking status and comorbidities.

The annual rate of decline in FVC, FVC % predicted, D_{LCO} and D_{LCO} % predicted both pre- and post-pirfenidone was calculated using PFT data at 12 months pre-treatment, baseline and 12 months post-treatment. In those patients that did not have PFTs performed at 12 months pre- or post-treatment, using two or more PFT data sets (over a period greater than 12 months) a line of best fit was created using Microsoft Excel, which was then used to estimate the annual rate of decline in lung function. The absolute change in FVC% and D_{LCO} % predicted was used rather than relative change.

Patients were stratified into slow or rapid decliner groups according to the rate of decline in FVC % predicted in the 12 months prior to them receiving pirfenidone. Patients were defined as being slow decliners if they had a rate of decline in FVC % predicted of less than 5%. If the rate of decline in FVC % predicted was 5% or greater, they were designated as a rapid decliner. 5% was used as a cut off as a 2-6%

annual decline in FVC has been suggested as being clinically meaningful and noticeable by a patient in terms of symptom change (23). It also split the two groups into equal numbers of patients.

Wilcoxon signed rank or Mann-Whitney test was used to compare numerical variables that were not normally distributed and t-test was used to compare numerical variables that were normally distributed. Data were analysed in GraphPad Prism 7.0a. Parametric data are presented as mean ± standard deviation, unless otherwise stated. Non-parametric data are presented as median and interquartile range (IQR). P values <0.05 were considered to be statistically significant.

Results

Study population

In total, 419 IPF patients treated with pirfenidone were identified. However, only patients who had FVC data for at least 12 months prior to starting pirfenidone, at baseline (within one month pre/post treatment) and at least 12 months post-treatment initiation were included. As a result, 384 patients were excluded from the study as they did not have lung function data sufficient for a full evaluation. 309 patients (80.5%) were excluded due to the absence of PFT data at least 12 months pre-pirfenidone. This was due to these patients starting pirfenidone within

12 months from diagnosis. 53 patients (13.8%) were excluded due to the absence of PFT data at least 12 months post-pirfenidone. Reasons for the absence of this data include discontinuation of pirfenidone (n = 20) and death (n = 14). In 19 patients the PFT data was absent as the data was collected within 12 months of the patient commencing pirfenidone. 22 patients (5.7%) were excluded as PFT data was not available within one month pre/post treatment. One patient was excluded from the analysis as there was a 48% improvement in FVC over a 12-month pre-treatment period which is inconsistent with clinical behaviour and likely secondary to improved spirometry technique. Therefore, 34 patients were included in the study. Out of the 34 patients, 13 had the annual rate of decline in FVC% and D_{LCO} % predicted imputed from a line of best fit.

At the time of starting pirfenidone, the 34 patients had a mean age of 69 years (range 54-83). 71% were male. Mean BMI was 28.2 (range 18.7-36.7). 59% were ex or current smokers. Mean FVC was 2.6 ± 0.56L, mean FVC % predicted was 71.1 ± 7.2%, mean D_{LCO} was 3.7 +/- 1.1 mmol/min/kPa and mean D_{LCO} % predicted was 43.6 +/- 10.8% prior to pirfenidone therapy. Chronic obstructive pulmonary disease (COPD) was a documented comorbidity in 12% of patients prior to the diagnosis of IPF and therefore could represent combined pulmonary fibrosis and emphysema syndrome. Table 1 shows the baseline patient characteristics in our cohort compared to the CAPACITY (2) and ASCEND (3) studies.

Table 1. Baseline patient characteristics compared to CAPACITY and ASCEND studies

Patient characteristics	Total cohort (n=419)	Cohort analysed (n=34)	CAPACITY (n=432)	ASCEND (n=278)
Mean age - years	70.1	68.8	66.8	68.4
Male sex – no. (%)	338 (80.7)	24 (70.6)	306 (70.8)	222 (79.9)
Former / current smoker – no. (%)	278 (66.3)	20 (58.8)	399 (92.4)	184 (66.2)
Mean FVC % predicted	68.6	71.1	75.2	67.8
Mean D_{LCO} % predicted	40.3	43.6	47.1	43.7

Decline in PFTs

Pirfenidone treatment resulted in no statistically significant change in the median (IQR) annual rate of decline in FVC (-150 (-315 − -47.5) ml/yr vs -55 (-340 − 45) ml/yr; n=34; p=0.35), FVC % predicted (-4.5 (-9.3 − -1.3) %/yr vs -1.2 (-7.2 − 3.3) %/yr; n=34; p=0.16), D_{LCO} (-0.49 (-0.97 − 0.0075) units/yr vs -0.55 (-0.84 − -0.11) units/yr; n=24; p=0.89) or D_{LCO} % predicted (-6.6 (-10.8 − 2.6) %/yr vs -6.2 (-9.5 − -1.2) %/yr; n=24; p=0.96). Figure 1 shows the annual rate of decline in FVC % predicted pre- and post-pifenidone.

In the rapid decliners, defined as annual rate of decline in FVC ≥5%, pirfenidone significantly reduced the median (IQR) annual rate of decline in FVC (-310 (-480 − -220) ml/yr vs 20 (-285 − 140) ml/yr; n=17; p<0.01) and FVC % predicted (-8.7 (-14.2 − -7.0) %/yr vs 2.0 (-7.1 − 6.0) %/yr; n=17; p<0.01). There was no significant change in the median (IQR) annual rate of decline in D_{LCO} (-0.44 (-1.6 − 0.005) units/yr vs -0.81 (-0.86 − -0.15) units/yr; n=9; p=0.89) or D_{LCO} % predicted (-9.0 (-15.2 − 1.1) %/yr vs -8.1 (-10.6 − -1.0) %/yr; n=9; p>0.99). Figure 2 demonstrates the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the rapid decliners.

In the slow decliners, defined as annual rate of decline in FVC <5%, there was a statistically significant increase in the mean annual rate of decline in FVC (-70 (-115 − 20) ml/yr vs -180 (-350 − -25) ml/yr; n=17; p=0.005) and FVC % predicted post-pirfenidone (-1.3 (-3.2 − 1.3) %/yr vs -5.0 (-8.3 − -0.35) %/yr; n=17; p=0.028). There was no significant

change in the median (IQR) annual rate of decline in D_{LCO} (-0.54 (-0.86 − 0.04) units/yr vs -0.46 (-0.71 − -0.05) units/yr; n=15; p=0.81) or D_{LCO} % predicted (-5.6 (-10.3 − 4.4) %/yr vs -4.9 (-8.0 − -0.5) %/yr; n=15; P>0.99). Figure 3 shows the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the slow decliners.

The baseline patient characteristics were similar between the rapid and slow decliner groups (table 2). Three patients in the rapid decliner group and four patients in the slow decliner group had either a dose reduction or a temporary discontinuation of pirfenidone due to side effects during the 12 months after commencing treatment.

Of the four patients with a documented co-morbidity of COPD, two were rapid decliners and
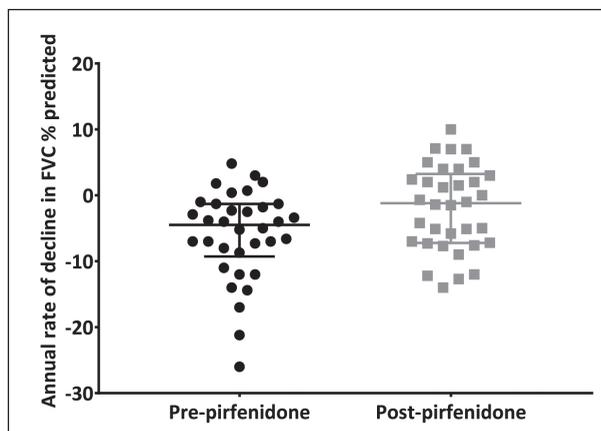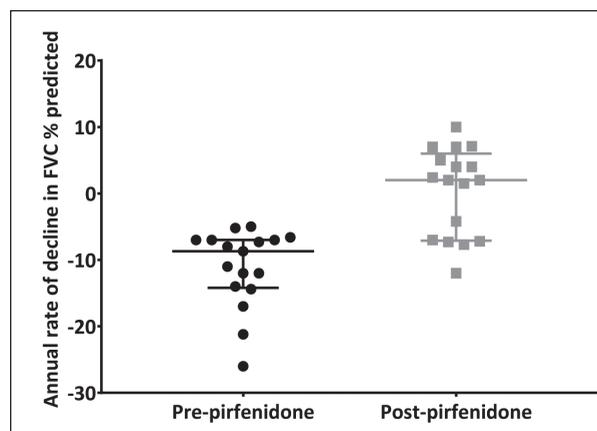
Fig. 2. Scatter plots (median and IQR) of the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the rapid decliners (p<0.01)

Fig. 1. Scatter plots (median and IQR) of the annual rate of decline in FVC % predicted pre and post pifenidone (p=0.16)
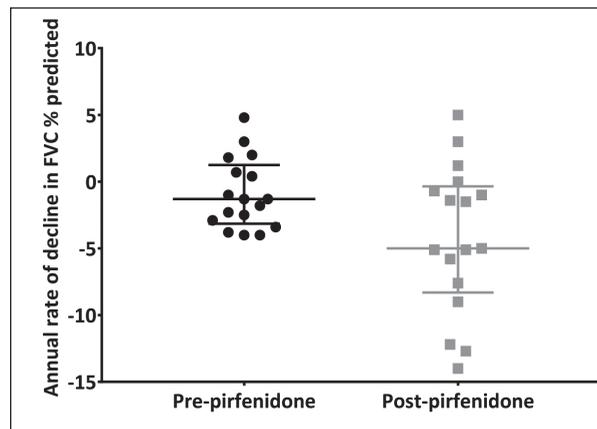
Fig. 3. Scatter plots (median and IQR) of the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the slow decliners (p=0.028)
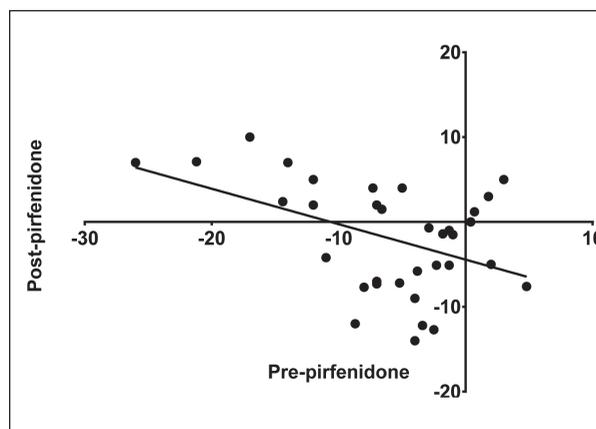
Table 2. Baseline patient characteristics of the rapid decliner and slow decliner groups (stratified using a pre-pirfenidone annual decline of FVC ≥5% versus <5%)

Patient characteristics	Rapid decliners	Slow decliners	p value
Mean age - years	68.9	66.9	0.45
Male sex – no. (%)	11 (64.7)	13 (76.5)	0.71
Former / current smoker – no. (%)	8 (47.1)	12 (70.6)	0.30
Mean FVC % predicted	70.4	71.7	0.62
Mean D_{LCO} % predicted	39.3	47.1	0.053

two were slow decliners. When these patients were removed from the above analysis there was no significant change to the results in terms of decline in FVC, FVC % predicted, D_{LCO} or D_{LCO} % predicted both overall and when stratified into slow or rapid decliner groups.

When the cohort of 34 patients were stratified into rapid and slow decliner groups using an annual rate of decline in FVC of ≥10% versus <10%, there was no statistically significant change in the median annual rate of decline in FVC or FVC % predicted pre- and post-pirfenidone in the slow decliners (n=26). However, in the rapid decliner group (annual rate of decline in FVC ≥10%) pirfenidone significantly reduced the median (IQR) annual rate of decline in FVC (-385 (-510 − -240) ml/yr vs 140 (50 − 280) ml/yr; n=8; p<0.01) and FVC % predicted (-14.2 (-20.2 − -12.0) %/yr vs 6.0 (2.1 − 7.1) %/yr; n=8; p<0.01). There was no statistically significant change in the median annual rate of decline in D_{LCO} or D_{LCO} % predicted pre- and post-pirfenidone in the slow decliners (n=20) or the rapid decliners (n=4).

Figure 4 is a linear regression XY graph of the annual rate of decline in FVC % predicted pre- and post-pirfenidone. The gradient of best fit is approximately -0.4 which means that for every 1% annual decline in FVC % predicted pre-treatment, there was a 0.4% greater response to pirfenidone. This is significantly non-zero with p=0.0084. Therefore, there is a significant negative correlation between the annual rate of decline in FVC % predicted pre- and post-pirfenidone.

Fig. 4. Linear regression XY graph of the annual rate of decline in FVC % predicted pre- and post-pirfenidone (p=0.0084)

DISCUSSION

This retrospective observational study from two tertiary referral centres for ILD in the North of England demonstrates the real world experience of pirfenidone treatment for a subset of patients with IPF in which lung function data was available at least 12 months pre- and post-treatment. IPF is generally a progressive disease with a variable clinical course which is often difficult to predict. Our data suggest that the rate of decline in FVC % predicted prior to starting pirfenidone can be used to stratify patients into slow (<5%/yr) and rapid decliners (≥5%/yr) and that the effect of pirfenidone is significantly different in these two groups. Our data demonstrate that pir-

fenidone significantly reduced the mean annual rate of decline in FVC % predicted and FVC in rapid decliners but not in slow decliners. In fact, there was a statistically significant increase in the mean annual rate of decline in FVC % predicted post-pirfenidone in the patients declining slowly. However, as demonstrated in figure 4, the FVC % predicted post-pirfenidone remained stable in the majority of the slow decliners. As pirfenidone treatment can be associated with a side effect profile it is important to attempt to identify those patients who will gain the best balance between benefit (in terms of reduced lung function decline) and potential harm (side effects). Therefore, we suggest that using a 5% annual rate of FVC decline cut off may be useful in making pirfenidone treatment decisions, especially in those patients where there are concerns regarding the benefit of treatment.

Nathan et al. have described, in post hoc analysis of the CAPACITY and ASCEND pooled data set, the inability of previous lung function to predict future lung function (24). This data analysis has been derived from static data points of FVC and FVC % predicted and has not considered rate of decline in FVC or FVC % predicted. However, our data analysis, although performed in much smaller numbers of patients, suggests that the rate of decline in lung function is an important consideration alongside static point measurement of FVC.

Three real life studies have shown similar results regarding the greater net effect of pirfenidone in IPF patients declining rapidly as compared with more slowly declining patients. A study by Okuda et al. demonstrated that patients who had the most severe decline in FVC (≥150 ml over a six-month period before starting pirfenidone) benefitted the most from treatment (10). Loeh et al. found that patients with an annual decline of FVC ≤10% prior to receiving pirfenidone remained stable with treatment, whereas those patients with an annual decline of >10% benefitted greatly from pirfenidone, with some patients experiencing an improvement in FVC (13). A similar outcome was demonstrated by Biondini et al. who also found that the beneficial effect from pirfenidone was greater in the patients with a pre-pirfenidone annual decline of FVC >10%, especially over the first six month treatment period (21). In addition to these studies, our results suggest that rapid decliners receive the most therapeutic benefit when the groups

are stratified using a pre-pirfenidone annual decline of FVC ≥5% versus <5% as well as ≥10% versus <10%.

This study was retrospective and therefore limited mainly by our access to PFT data, both pre- and post-initiation of pirfenidone treatment, and the variation in testing and timing that often follows from usual clinical practice. Across the two centres, there were 419 IPF patients treated with pirfenidone over the study period. However, due to the lack of PFT data, 384 patients (92%) were excluded. This was mainly due to the absence of PFT data pre-pirfenidone, as many patients would have commenced treatment within 12 months of diagnosis. These patients that were excluded are more likely to have either rapidly progressive disease or a delayed diagnosis which is a potential source of bias. However, as illustrated in table 1, the lung function at the time of commencing pirfenidone was similar between the total cohort (n = 419) and the cohort with sufficient PFT data for analysis (n = 34). Another potential source of bias is the exclusion of patients that died or discontinued pirfenidone within 12 months of starting treatment.

Following initiation of pirfenidone, there was no statistically significant reduction in the median annual rate of decline in FVC or FVC% predicted in the total cohort. This may be due to the statistically significant increase in the median annual rate of decline in FVC and FVC% predicted post-pirfenidone observed in the slow decliner group. This has not been reported in previous studies of pirfenidone in IPF patients and is an interesting finding. However, this result is based on a small sample of a larger data set which is prone to bias and thus has a chance of being spurious. Therefore, it does not represent sufficient evidence for IPF patients with a slow rate of decline in FVC to be denied pirfenidone. The relatively small number of patients in our study necessitates caution when extending our findings to IPF patients in general and further prospective clinical studies, including larger numbers of patients are required before drawing any firm conclusions.

It could be argued that our data can be interpreted through reference to the statistical concept of 'regression to the mean'. This concept describes a bigger effect of a treatment in groups where high numbers of events are present e.g. the outcome of treatment of patients with high rate of decline in FVC will be greater than outcomes of treatment in patients with

slower FVC decline (less events). Although there is no specific statistical test that can confirm or refute this, the significant negative correlation between the annual rate of decline in FVC % predicted pre- and post-pirfenidone, demonstrated in figure 4 suggests that this is not the case.

In conclusion, we demonstrate a greater net effect of pirfenidone in patients declining rapidly as compared with more slowly declining patients. We suggest that using an incident rate of decline in FVC of <5% per year (slow decliners) and ≥5% per year (rapid decliners) may be useful in counselling patients with regard to treatment. However, we recognise the limitations of the study and suggest that larger studies are needed to confirm our findings before making significant changes to the routine management of IPF patients.

References

1. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35:821-829.

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

3. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2083-2092.

4. National Institute for Health and Care Excellence. Pirfenidone for treating idiopathic pulmonary fibrosis. In NICE Technology Appraisal Guidance (TA282); National Institute for Health and Care Excellence: Manchester, UK, 2013.

5. National Institute for Health and Care Excellence. Nintedanib for treating idiopathic pulmonary fibrosis. In NICE Technology Appraisal Guidance (TA379); National Institute for Health and Care Excellence: Manchester, UK, 2016.

6. Kreuter M. Pirfenidone: an update on clinical trial data and insights from everyday practice. Eur Respir Rev 2014; 23:111-117.

7. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. Eur Respir J 2016; 47:243-253.

8. Arai T, Inoue Y, Sasaki Y, et al. Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis. Respir Investig 2014; 52:136-143.

9. Sakamoto S, Itoh T, Muramatsu Y, et al. Efficacy of pirfenidone in pa-

tients with advanced-stage idiopathic pulmonary fibrosis. Intern Med 2013; 52:2495-2501.

10. 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 2013; 107:1431-1437.

11. Oltmanns U, Kahn N, Palmowski K, et al. Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. Respiration 2014; 88:199-207.

12. 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 2014; 108:224-226.

13. Loeh B, Drakopanagiotakis F, Bandelli GP, et al. Intraindividual response to treatment with pirfenidone in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2015; 191:110-113.

14. Harari S, Caminati A, Albera C, et al. Efficacy of pirfenidone for idiopathic pulmonary fibrosis: an Italian real life study. Respir Med 2015; 109:904-913.

15. Wijsenbeek MS, Grutters JC, Wuyts WA. Early experience of pirfenidone in daily clinical practice in Belgium and the Netherlands: a retrospective cohort analysis. Adv Ther 2015; 32:691-704.

16. Konishi S, Arita M, Ito I, et al. Composite physiologic index, percent forced vital capacity and percent diffusing capacity for carbon monoxide could be predictors of pirfenidone tolerability in patients with idiopathic pulmonary fibrosis. Intern Med 2015; 54:2835-2841.

17. Bando M, Yamauchi H, Ogura T, et al. Clinical experience of the long-term use of pirfenidone for idiopathic pulmonary fibrosis. Intern Med 2016; 55:443-448.

18. Sköld CM, Janson C, Elf AK, Fiaschi M, Wiklund K, Persson HL. A retrospective chart review of pirfenidone-treated patients in Sweden: the REPRIS study. Eur Clin Respir J 2016; 3:32035.

19. Salih GN, Shaker SB, Madsen HD, Bendstrup E. Pirfenidone treatment in idiopathic pulmonary fibrosis: nationwide Danish results. Eur Clin Respir J 2016; 3:32608.

20. Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N. Real world experiences: pirfenidone and nintedanib are effective and well tolerated treatments for idiopathic pulmonary fibrosis. J Clin Med 2016; 5:78.

21. Biondini D, Balestro E, Lacedonia D, et al. Pretreatment rate of decay in forced vital capacity predicts long term response to pirfenidone in patients with idiopathic pulmonary fibrosis. Sci Rep 2018; 8:5961.

22. 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 2011; 183:788-824.

23. du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis. Test properties and minimally clinically important difference. Am J Respir Crit Care Med 2011; 184:1382-1389.

24. Nathan SD, Albera C, Bradford WZ, et al. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax 2016; 71(5):429-435.