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SHORT COMMUNICATION

Real world experiences: Pirfenidone is well tolerated in patients with idiopathic pulmonary fibrosis

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Summary
Idiopathic pulmonary fibrosis (IPF) is a debilitating condition with life expectancy of two to five years from diagnosis. Treatment strategies for IPF are disappointingly limited and pirfenidone is currently the only licensed drug that has been shown to reduce the decline in forced vital capacity (FVC) at six months. We demonstrate our experience in prescribing pirfenidone in a single centre observational study of forty patients involved in a named patient programme (NPP) from September 2011 to January 2013.

We demonstrate that improved adherence and compliance can be achieved by specialist nurse and clinician review, support and education of the patient. Twenty three of 40 (58%) patients experienced predominantly gastrointestinal adverse effects. Importantly we have enhanced patient adherence and compliance from an initial discontinuation rate of six patients (15%) at the beginning of the study to a zero discontinuation rate in the subsequent ten months.

This study shows that in the real world pirfenidone is well tolerated and with expert regular specialist review adherence can be optimised and improved.
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Introduction

Idiopathic pulmonary fibrosis (IPF) is a debilitating condition with life expectancy of two to five years from diagnosis. Treatment strategies for IPF are disappointingly limited and pirfenidone is currently the only licensed drug that has been shown to reduce the decline in forced vital capacity (FVC) at six months [1]. In the United Kingdom pirfenidone has undergone National Institute of Health and Clinical Excellence (NICE) consultation for approval in its use for patients with IPF. Pirfenidone is currently only prescribed in selected specialist centres on a named patient programme (NPP).

Methods

This was a single centre observational study of patients involved in the NPP. Inclusion criteria included a multidisciplinary team (MDT) diagnosis of IPF as per American Thoracic Society/European Respiratory Society (ATS/ERS) criteria [2], FVC greater than 50% and/or carbon monoxide diffusing capacity (DLCO) greater than 35% predicted.

Patients consented to the NPP. All patients had baseline pulmonary function tests (PFTs), full blood count (FBC) and liver function tests (LFTs) prior to commencing pirfenidone. Pirfenidone was prescribed as per manufacturer's recommendations. Patients were reviewed at monthly intervals for the first six months, and then three monthly thereafter, if stabilised on treatment. Each clinical review involved confirmation of the dose of pirfenidone, any side effects in the preceding months, chest infections, hospital admissions and new medication. FBC and LFTs were checked at each clinical review. PFTs were performed at baseline and three monthly intervals after treatment commencement. In some patients we had pre-pirfenidone PFTs which gave us the opportunity to compare decline in FVC and DLCO pre- and post-commencement of pirfenidone in a limited numbers of patients.

We retrospectively analysed the data from forty patients treated with pirfenidone from September 2011 to January 2013. Data were analysed using GraphPad Prism v5. Where indicated data was compared using unpaired two tailed *t*-tests.

Results

At commencement of pirfenidone the mean age was 65.8 years (range 48—80) with 70% males. Average baseline FVC and DLCO was 77.3% (range 46—146%) and 42.4% (range 14—81%) respectively. Fifteen (37.5%) patients had an FVC greater than 50% with baseline DLCO of less than 35%. Seven (18%) patients were receiving long term oxygen therapy, four (10%) had ambulatory oxygen and 29 (72%) received no oxygen. At commencement of pirfenidone seven (17%), five (12%) and nine (23%) patients were taking prednisolone (average 10 mg), N-acetylcysteine (NAC) or both prednisolone and NAC respectively. During this time period twelve (30%) patients died, of which 9 (75%) had a baseline DLCO of less than 35%. Ten patients died due to progression of their IPF, one due to a diagnosis of lung cancer and one due to

exacerbations. These patients had significantly reduced duration of treatment (18.4 ± 2.4 vs. 42.3 ± 4.7 weeks $p = 0.0017$) and severer disease as measured by baseline DLCO compared to survivors ($30.2 \pm 2.2\%$ vs. $48.1 \pm 2.9\%$ $p = 0.0002$). A total of 21 (52%) patients continued treatment to the end of the study period and six (15%) discontinued treatment due to adverse effects.

Twenty three of 40 (58%) patients experienced adverse effects. Twelve (52%) patients experienced one adverse effect, seven (31%) experienced two and four (17%) patients experienced three or more adverse effects. The majority of adverse effects were gastrointestinal in nature (87%). Other adverse effects included exacerbations of IPF (12.8%), rash (10.3%) and pneumothorax (2.6%) Adverse effects occurred within an average of 8.1 weeks (range 1.5—34) and in those patients with lower body mass index
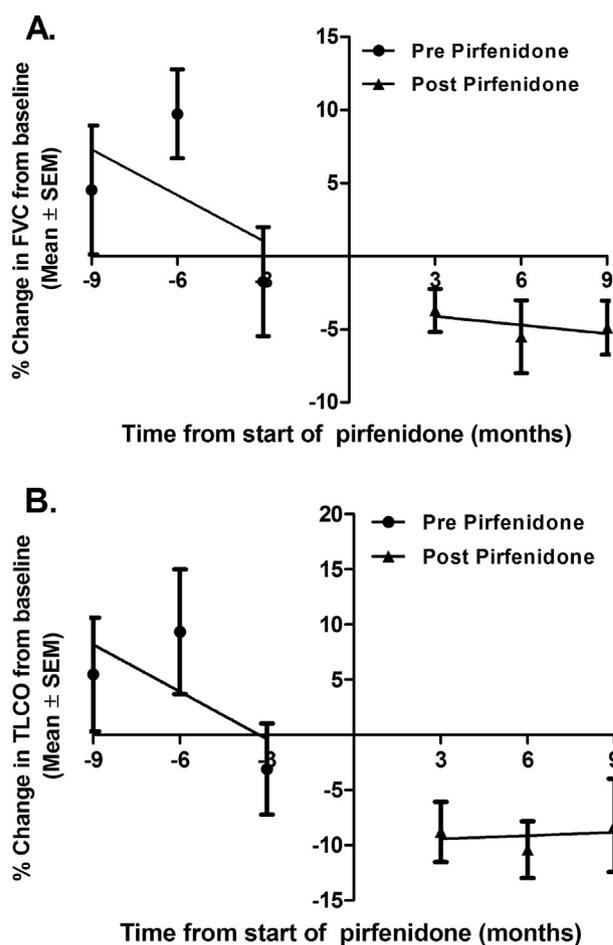
Figure 1 **There appears to be a reduction in FVC and DLCO decline after commencement of pirfenidone.** Pulmonary function tests were performed at three, six and nine months pre- and post-pirfenidone commencement. The percentage change in FVC and DLCO was calculated from baseline values at commencement of pirfenidone. Data shown are mean ± SEM at three, six and nine months pre- and post-pirfenidone commencement (*n* = 14, 14 and 11 pre-pirfenidone and *n* = 26, 23 and 15 post-pirfenidone respectively). The gradients of the slopes were calculated using linear regression analysis using Prismv5 software.

(BMI) (26.4 ± 0.79 vs. 30 ± 1.18 p = 0.014). Of these adverse effects nine (39%) were self-limiting and resolved with simple measures. Three (13%) resolved after a reduction in dosage, in three (13%) patients pirfenidone was restarted after the adverse effect settled and two (9%) patients died due to their exacerbation. Only four patients experienced mild abnormalities in LFTs that resolved spontaneously on repeated testing without any alteration of medication. Despite similar incidence of adverse effects, patients with DLCO of less than 35% were less likely to continue treatment (29% vs. 71%) and more likely to discontinue treatment due to their adverse effects (67% vs. 33%).

During the first six months of recruitment six (15%) patients discontinued treatment due to adverse effects. In the later ten months we had no discontinuations. This has been attributed to a number of factors. Patient factors included simple measures such as use of sun protection and taking the pirfenidone capsules at the start, middle and end of a meal in an attempt to minimise side effects. We found that the majority of adverse effects occurred within the first eight weeks of treatment and as a result monthly specialist nurse review for the first three months, to assess and reinforce adverse effect avoidance measures was, we feel, paramount to the success of our increased adherence. Patients were also given a contact number and encouraged to speak to a specialist nurse if they experienced any adverse effects. This allowed us to act promptly and either reduce, temporarily discontinue or administer further medication in order to alleviate the adverse effects.

At six and nine months before and after pirfenidone commencement we observed a reduction in the decline of mean percentage change of FVC and DLCO at start of treatment. At nine months there was a difference in gradient of decline before and after pirfenidone commencement of −1.043 ± 1.605 vs. −0.197 ± 0.231 for FVC decline and −1.427 ± 1.568 vs. 0.1 ± 0.367 for DLCO decline (Fig. 1).

Conclusion

Our data regarding reduction in decline of FVC and DLCO is encouraging and may support the previous efficacy data from clinical trials. However, we acknowledge the major limitations of drawing any statistical conclusions from this retrospective observational data with small patient numbers, lack of appropriate controls and incomplete pulmonary function data. We demonstrate that, compared to patients with less severe disease, patients with a DLCO < 35% are more likely to discontinue treatment despite a similar incidence of adverse effects, presumably due to a lack of beneficial effect on symptoms. We believe that regular specialist nurse support, advice and education, particularly in the first months of treatment when adverse effects are likely to occur, is paramount to the optimal adherence and compliance of pirfenidone.

Disclosure

References

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