BMJ Open Respiratory Research

Pirfenidone: is it tolerable?

Abigail Lara, Marvin Schwarz

To cite: Lara A, Schwarz M. Pirfenidone: is it tolerable?. *BMJ Open Resp Res* 2016;**3**: e000124. doi:10.1136/bmjresp-2015-000124

Received 30 November 2015
Accepted 16 December 2015

Linked

▸ http://dx.doi.org/10.1136/bmjresp-2015-000105

Division of Pulmonary Sciences & Critical Care Medicine, University of Colorado Denver, Aurora, Colorado, USA

Correspondence to
Dr Marvin Schwarz; marvin.schwarz@ucdenver.edu

Idiopathic pulmonary fibrosis (IPF) remains the commonest and most lethal of all the fibrotic lung diseases. Until recently, clinical studies identifying effective treatments have largely been lacking. Two agents, pirfendione and nintedanib have recently demonstrated clinical efficacy in slowing the rate of physiological decline in patients and improve progression-free survival after 52 weeks of treatment in those who were rigorously diagnosed with IPF.[1–3] Pirfendione, an oral pyridine compound, exerts it's effect by targeting multiple pathways that have been implicated in the pathophysiology of IPF.[4] The clinical efficacy of pirfendione was evaluated in several phase 3 randomised control trials, which led to the US Food and Drug Administration (FDA) approval for use and has demonstrated a clear improvement in physiological metrics of disease as well as clinically relevant outcomes including reduction in mortality as well as decrease in IPF associated exacerbations and death. Though pirfendione has clearly been proven as a treatment for IPF, the long-term side effects and tolerance of taking the medication has not been clearly demonstrated.

The article by Lancaster *et al*,[5] seeks to describe the safety profile and long-term patient tolerance by performing an integrated analysis of all patients included in the previously published phase 3 studies, CAPACITY (studies 004 and 006) and ASCEND (study 016) as well as two ongoing open-label studies, RECAP (study 012) and study 002. The resultant analysis was performed using a large, well-defined population (n=1299) with mild-moderate IPF. The drug safety profile was assessed by determining cumulative total exposure, as expressed as person-exposure years (PEY), resulting in more than 3000 PEY over a range of 1 week–9.9 years.

In keeping with the previously published studies, the integrated analysis demonstrated gastrointestinal events (nausea, diarrhoea, dyspepsia and vomiting) and rash were the most common adverse events and nearly all patients treated with pirfenidone experienced a treatment adverse event. The severity of these events were considered mild to moderate and rarely led to treatment discontinuation. Interestingly, the rate at which patients discontinued treatment due to an adverse event was demonstrably higher in the integrated population (38.1%) in comparison to the pooled pirfenidone group in the phase 3 trial (14.6%). The most common event that lead to treatment discontinuation was progression of IPF (11.5%). In regard to the safety profile, alterations in liver enzymes were not significantly different in the integrated population.

The study duration in CAPACITY and ASCEND were time limited to 72 and 52 weeks, respectively. The article by Lancaster *et al*, provided evidence of the long-term safety profile of pirfenidone of up to nearly 10 years of use, determined by treatment adverse events relative to the PEY, in which they demonstrated that the integrated population did not show an increase risk of liver toxicity with longer duration of use.

The study provides a framework for which clinicians and patients can utilise in the decision-making process to begin therapy for IPF. Not only does this study provides long-term experience that supports the previously published reports that pirfenidone is relatively well tolerated, the integrated population that was included in this study allows for applicability to the general population of patients with IPF. The obvious limitations of the study by Lancaster *et al*, cannot be ignored, namely the inclusion of open label studies without a control group. Further, there are inherent concerns of applying results of an integrated analysis to the general population of patients with a relatively rare disease such as IPF that may fall outside of the deliberated restriction of the inclusion criteria of the studies.

A cure for IPF remains elusive, however, for the first time clinicians have been provided with therapies that can slow the clinical course of this devastating disease, but it is yet to be determined if it improves mortality.

This still offers hope for patients in the long-term. However, it remains to be seen if the clinical efficacy of pirfenidone can be recapitulated in fibrotic lung diseases other than IPF thus providing further testament to it is strength as a treatment modality.

Correction notice This article has been corrected since it was published Online First. Reference 5 has now been updated.

Contributors All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing or revision of the manuscript.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES

1. Richeldi L, Costabel U, Selman M, *et al*. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011;365:1079–87.
2. Noble PW, Albera C, Bradford WZ, *et al*. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011;377:1760–9.
3. King TE, Bradford WZ, Castro-Bernardini S, *et al*. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–92.
4. Kim ES, Keating GM. Pirfenidone: a review of its use in idiopathic pulmonary fibrosis. *Drugs* 2015;75:219–30.
5. Lancaster L, *et al*. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: Integrated analysis of cumulative data from 5 clinical trials. *BMJ Open Resp Res* 2016;3:e000105. doi:10.1136/bmjresp-2015-000105