

# Pirfenidone should be prescribed for patients with idiopathic pulmonary fibrosis

Gisli Jenkins

Pirfenidone works. There have been four randomised placebo-control trials of pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF); a phase II and phase III study in Japan, and two international multicentre phase III studies.<sup>1–3</sup> In all four studies, patients treated with pirfenidone had slower rates of decline in lung volume (vital capacity (VC) in the Japanese studies and forced vital capacity (FVC) in the international studies) than placebo, and in three studies, the results were statistically significant. National Institute of Clinical Excellence (NICE) agrees that pirfenidone has a 'modest but measurable effect on slowing the decline in lung function'.<sup>4</sup> Therefore, whether patients receive pirfenidone depends on whether pirfenidone works enough to justify its cost.

IPF is a chronic progressive disease of unknown aetiology, it is fatal with a median survival of approximately 3 years,<sup>5</sup> or less than one electoral cycle. No therapy has been proven to improve survival. Despite the absence of good evidence, various combinations of N-acetylcysteine (NAC), prednisolone and azathioprine have been used for many years to treat patients with IPF. In the early 1990s, a small study suggested that prednisolone and azathioprine might be beneficial,<sup>6</sup> and the initial British Thoracic Society (BTS) guidelines for the treatment of cryptogenic fibrosing alveolitis (as IPF was then known) recommended this therapy.<sup>7</sup> In 2005, the Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual (IFIGENIA) study demonstrated that NAC might be beneficial in IPF.<sup>8</sup> However, this study was criticised at the time for including azathioprine and prednisolone in both the placebo and treatment arms. The inclusion of this faux placebo lead some, possibly correctly, to suggest that NAC was inhibiting the adverse effects of prednisolone and azathioprine, rather than possessing any direct antifibrotic effect. The

2008 BTS IPF guidelines<sup>9</sup> implicitly recommended treatment with triple therapy, although this advice has been modified since the publication of the Panther study.<sup>10</sup> The primary justifications for using these therapies were: the possibility of benefit in some patients; low cost; and, at least for NAC, lack of major adverse effects.

Pirfenidone, unlike previously recommended therapies, has demonstrated significant improvements in lung function compared with placebo in randomised controlled trials (RCTs). Furthermore, pirfenidone improves progression-free survival,<sup>11</sup> 6 min walking distance,<sup>3</sup> and reduces acute exacerbations of IPF.<sup>1</sup> None of the studies were powered to assess mortality but, overall, 0.75% of patients (3/406) receiving pirfenidone died during the studies compared with 3.8% of patients receiving placebo (12/312). In the recent interim analysis of the Panther study, 1.3% of patients receiving placebo (1/77) had died compared with 10.3% of patients receiving triple therapy (8/78).<sup>12</sup> Pirfenidone causes dermatological (photosensitivity) and gastrointestinal (dyspepsia, diarrhoea, vomiting and anorexia) symptoms, and a slight increased risk of neurological disturbance (dizziness, fatigue, insomnia and anxiety), leading to a 15.7% drop-out rate in patients receiving pirfenidone in clinical trials, compared with 8.9% of patients receiving placebo.

So are these effects worth the cost? The absence of effective therapy suggests the average cost of treatment for a patient with IPF should be relatively low: single-agent NAC comes in at just over £200/year/patient; treatment is predominantly outpatient based; and high mortality rates mean treatment duration is short. NICE estimates outpatient treatment costs for IPF with best supportive care at £800 per year,<sup>4</sup> although estimates from claims databases in the USA suggest the cost of IPF closer to US\$17 000 for an outpatient.<sup>13</sup> NICE has calculated the incremental cost-effectiveness ratio (ICERs) at £36 327 per quality adjusted life years (QALY) gained, compared with best supportive care (using the remarkably low UK estimate), but only £16 560 per QALY

gained compared with triple therapy.<sup>4</sup> While at first glance pirfenidone seems expensive, it is only about twice the price of triple therapy, so maybe it is not quite as expensive as previously thought. The current threshold for NICE approval is between £20 000 and £30 000 per QALY. The QALY is an estimate of effectiveness based on both quality-of-life, using primarily the EuroQol ED-50 questionnaire, as well as life expectancy. It is clear the QALY is not going to favour pirfenidone, because the clinical trials were not powered to detect changes in mortality, nor did they measure the ED-50 scores. Furthermore, a major limitation of the QALY is that it only considers the cost-effectiveness of a therapy in relation to the patient taking the drug, excluding effects on third parties, such as relatives and carers, and the global economic benefits of bringing novel therapies to market.

Are effects on lung physiology worth paying for? Change in FVC is an accepted marker of mortality and disease progression in IPF.<sup>14</sup> It is a clinically useful measurement; it was the primary endpoint in the CAPACITY study, but it has little impact on the QALY. Some argue that all phase III studies in IPF should be powered to detect mortality as the primary endpoint.<sup>15</sup> While powering clinical trials for mortality to demonstrate harm would not require large trials, a study demonstrating improved survival is likely to need nearly 2600 patients followed for 5 years.<sup>16</sup> This would exponentially add to clinical trial costs, which would ultimately have to be passed on to the consumer and, thus, reduce the cost-effectiveness of the drug (because performing the trial does not improve efficacy of a drug, it merely demonstrates whether the drug has efficacy or not). Therefore, if NICE do not consider change in FVC as an endpoint worth paying for, it means clinical trials in IPF, and thus drugs for IPF, will become considerably more expensive.

IPF is the Cinderella disease of the Cinderella speciality (see table 1), killing nearly 4000 people in the UK each year; therefore, more people are dying of IPF than of many cancers, including cervical, ovarian, pancreatic and renal cancer. Within the field of respiratory medicine, the ugly sisters of asthma and chronic obstructive pulmonary disease (COPD) take a lion's share of resources. Seretide is the biggest single drug expenditure in the National Health Service (NHS), costing £366.2 million per year.<sup>17</sup> The NICE guidelines for COPD treatment lay out the standards for use of combination

**Correspondence to** Dr Gisli Jenkins, Nottingham Respiratory Research Unit, University of Nottingham, Clinical Sciences Building, City Hospital Campus, Hucknall Road, Nottingham NG5 1PB, UK; gisli.jenkins@nottingham.ac.uk

**Table 1** Estimates of spending on health care, medical research and professional football

Activity	Annual spend (£)
Total UK healthcare spending <sup>25</sup>	121.5 billion
Cost of cardiac care to NHS <sup>26</sup>	15 billion
UK spending on non-acute secondary care <sup>25</sup>	7 billion
Cost of respiratory care to NHS <sup>27</sup>	3 billion
Premier League Football wages <sup>28</sup>	1.6 billion
CRUK research budget <sup>22</sup>	504 million
Atorvastatin cost <sup>17</sup>	322 million
Manchester United wage bill <sup>28</sup>	153 million
Average Premier League player salary <sup>28</sup>	1.4 million
BLF research fund <sup>29</sup>	1 million
BLF allocation to IPF <sup>29</sup>	800 000 (total since 1985)
Estimated cost of outpatient IPF care <sup>4</sup>	800

IPF, idiopathic pulmonary fibrosis; NHS, National Health Service; CRUK, Cancer Research UK; BLF, British Lung Foundation.

steroid/long acting beta agonist (LABA), and long-acting muscarinic antagonist (LAMAs) inhalers, but large numbers are prescribed outside of these criteria. However, the unit cost is relatively small, thus, few questions are asked, and the result is a multimillion pound bill to the NHS picked up by IPF patients. If every patient with IPF in the UK were to receive pirfenidone, it would cost little more than the annual cost of tiotropium (£113 million).<sup>17</sup> In the current economic climate of flatlining NHS expenditure, pirfenidone could be incorporated into respiratory budgets by guideline-driven, generic prescribing of current inhaled therapy before we even have to start looking toward big spending specialties such as cardiology.

Not every patient, however, will need to receive pirfenidone. In a genetically heterogeneous group, such as the UK population or patients involved in an RCT, there is a graded response from a small minority of dramatic responders, to the many who do not respond. Those who believe in 'precision medicine', including Lord Darzi, realise that it is the few, potentially identifiable, 'responders' within the population that skew the treatment effect. The same is true of, and also much more obvious for, adverse effects. This applies to all drugs, and ideally, we could predict responders before giving therapy on the basis of known mechanism of action and stratification against a molecular marker. Unfortunately, pirfenidone is a 'good old-fashioned' drug, and nobody really knows how it works. However, because of its known effect on lung function, what could and should happen (and what clinicians have been doing for decades), is that therapy would be provisional upon disease progression

and response; further reducing the financial burden of pirfenidone.

The introduction of pirfenidone should be the first small step in a long-term strategy for improving the outlook for patients with IPF. The strategic goal should be to follow the model proposed by the National Cancer Research Institute, namely improved patient care through research. This has generated small incremental benefits in outcome, rather than any large paradigm shift, which ultimately, over time, revolutionised outcomes for many cancers. The last decade has seen the blossoming of such a strategy. At the start of the new millennium, there had been four studies that had recruited 114 patients into clinical trials. However, since 2000, there has been an explosion in the number of patients with IPF entered into clinical trials (3849 patients entered into 15 published trials). This has been driven, in part, by the rising incidence of IPF, up by 30% in the last decade,<sup>18</sup> in part, due to networks, such as IPFNet in the USA and, in part, due to pharmaceutical interest in fibrosis. This profusion of clinical trials has generated huge swathes of data that has improved our understanding of the natural history of IPF, exemplified by the recognition of the 'acute exacerbation' as the most dramatic and devastating complication of IPF, with a 30-day mortality of around 70%. The trials have also demonstrated that some of our accepted, if unsubstantiated, therapies were, at best, futile and, at worst, harmful.<sup>12–19</sup> Finally, a few trials have suggested that specific antifibrotic therapies may be effective.<sup>3–20</sup> IPF research has reached the point that breast cancer research arrived at in the early 1970s, when patients had the enviable 5-year survival rate of 52% (current 5-year survival for IPF is around 25%), but through

incrementally effective therapies, 5-year survival had reached 85% by the year 2009.<sup>21</sup>

The dramatic improvements seen in cancer outcomes come at a cost. In 2010, the National Cancer Research Institute in the UK spent £100 million on breast cancer research, up from £45 million in 2002,<sup>22</sup> whereas UK academic institutions might possibly spend £1 million per annum on IPF research. However, Intermune, the worldwide licenced manufacturer of pirfenidone, has spent an average of \$77 million per annum on IPF R&D in the last 3 years.<sup>23</sup> Pharmaceutical company interest in antifibrotic therapies has never been greater, highlighted by an editorial in *Nature Biotechnology*.<sup>24</sup> This is because there is widespread belief within the pharmaceutical industry that fibrotic processes are amenable to therapy, and that investment costs can be recovered. This will undoubtedly lead to improvements in patient care. These development costs have to be recovered; the issue is how we value, and reimburse, these costs. Failure to reimburse therapies that have been shown to be effective could dramatically hinder market confidence, with knock-on effects to the UK economy, and future patient care; certainly that is a view that Germany, France, Italy, Canada and others seem to have taken.

In a disease with a limited evidence base, only one drug, pirfenidone, has been shown to have a beneficial effect on the clinical progression of IPF. The only real arguments against the use of pirfenidone are its cost and the relevance of change in FVC as an endpoint for IPF. However, the costs of pirfenidone are not as high as imagined when placed in the context of treatment for respiratory disease generally, and could easily be accommodated through generic prescribing and adherence to guidelines. Furthermore, demonstrating efficacy against a marker of disease progression, such as FVC, in a chronic progressive disease characterised by loss of lung volume has the advantage of being able to determine response in individual patients avoiding the need to treat all-comers.

Therefore, I believe pirfenidone should be offered to patients with mild to moderate IPF, who have progressive disease, and show evidence of response at 6 months. The effect of denying access to the ONLY treatment that has ANY efficacy signal in an IPF patient population, a group that has been systematically underfunded for decades despite a prognosis worse than most cancers, would devastate the IPF community.

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