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Pirfenidone for IPF: pro/con debate; the 'con' viewpoint

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Improving outcomes for patients with idiopathic pulmonary fibrosis (IPF) remains a major unmet healthcare need—in this, we entirely agree with the 'pro' debate article by Gisli Jenkins.[1] In this regard, the efforts of drug companies in developing novel drugs and collaboration with expert clinical investigators in the field of IPF in wanting to demonstrate the therapeutic efficacy for patients with IPF are commendable.

Unfortunately, several clinical trials of novel therapy for IPF have yielded negative results. In 1999, the therapeutic potential of pirfenidone as the first antifibrotic pharmacologic agent with promises/hopes that it would improve outcomes for IPF patients was demonstrated in a phase II study.[2] Some 13 years later, initial enthusiasm is being questioned—hence, the rationale for this pro/con debate. In this article, it is our aim to provide a balance to Dr Gisli Jenkins's pro article,[1] and we hope to provide the readers of this debate a balanced view of the topic. Undoubtedly, the reader will realise that the truth probably exists between the two ends of this polarised academic debate. We believe that the clinician must assess the benefits and risks of pirfenidone treatment by addressing the following specific issues.

IPF HAS COMPLEX PATHOPHYSIOLOGY

Current evidence suggests that in a genetically predisposed person, IPF is manifested as a result of an aberrant response to an unidentified alveolar epithelial injury. Theories speculate that IPF results from abnormal wound-healing response which results in a persistently abnormal epithelial repair that promotes fibroblast proliferation generating a reticulum of activated fibroblasts and collagen which progressively restructures the lung architecture.[3 4] In addition to myofibroblast foci formation and epithelial cell injury, there is variable evidence of inflammation as evidenced by increased macrophage and neutrophil counts,[5 6] intra-alveolar coagulapathy,[7] and the formation of new blood vessels in the IPF lung.[8] Our understanding of these processes is still very limited, but it is apparent that unless the pathophysiologic processes are effectively targeted by a new drug for IPF, it is

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unlikely that one drug will be successful on its own in tackling this complex and dynamic pathophysiological process.[9]

HOW MAY PIRFENIDONE INFLUENCE THE PATHOPHYSIOLOGY OF IPF?

The specific mechanistic reasons for pirfenidone as an antifibrotic agent, and the exact receptor for pirfenidone is unknown, which is a surprise in the modern molecular age of drug development. Pirfenidone has been said to be antifibrotic due to actions in blocking the effects of TGF-β upon fibroblasts.[10] In animal models, pirfenidone blocks bleomycin-induced pulmonary fibrosis, but this is a very flawed model of IPF.[11] However, in animals, pirfenidone also blocks fibrosis in liver fibrosis, renal sclerosis and sclerosing dermatosis models.[12] In addition, it has been suggested that pirfenidone has anti-inflammatory properties, so the exact mechanism of any benefit for pirfenidone in IPF is currently unclear.[13]

CLINICAL TRIALS SHOW EFFECTS OF PIRFENIDONE ARE SMALL, AND SOME STUDIES REVEAL CONFLICTING RESULTS

Taniguchi *et al* showed a significant difference in VC decline between the placebo group (−0.16 litre) and the 1800 mg/day pirfenidone group (−0.09 litre) at week 52 in patients with IPF in Japan. The absolute treatment effect after 1 year was 0.07 litre. Differences between the two groups were also observed in progression-free survival which is partly dependent on FVC.[14] In a preceding Japanese study, Azuma *et al* showed their primary endpoint (exercise-induced desaturation) was no different with pirfenidone treatment, but change in VC was significantly different at 9 months (but not at 6 months) with a lower number of patients having acute exacerbation in the pirfenidone group.[15] Meta-analysis of these two trials showed a favourable effect on decline in FVC of 0.08 litre after 12 months of treatment.

The two CAPACITY studies have shown conflicting results—only one of the trials yielded positive results based on the chosen primary endpoint—that is, the change in FVC. In CAPACITY-1, pirfenidone demonstrated a statistically significant difference in mean change in per cent predicted FVC at 72 weeks (absolute difference 4.4% between the pirfenidone and placebo groups), but in CAPACITY-2 there was no significant difference between groups (absolute difference 0.6% in favour of pirfenidone). However, there was a statistically significant difference in mean change in per cent-predicted FVC in a pooled analysis of the two studies (absolute difference 2.5% in favour of pirfenidone).[16]

The patient population that was enrolled in the clinical trials in Japan was a selected population which demonstrated an oxygen desaturation in an unvalidated exercise test. The observed findings were in a subgroup of patients who were different than the patients enrolled in the CAPACITY I and II trials. In none of the currently reported clinical trials with pirfenidone did the patients demonstrate improvement in quality of life, symptoms and/or survival. The episodes of acute exacerbations that were felt to be higher in the placebo group compared with those receiving pirfenidone in the Japanese phase II trial[15] were not adjudicated, and this was not confirmed in subsequent phase III trials.[14]

Our interpretation of these trials is that, at best, pirfenidone monotherapy is weakly efficacious in IPF in terms of effects on lung function decline. This was also the view held by an international panel of experts representing the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and the Latin American Thoracic Society, who recommended against routine treatment with pirfenidone—it was a "weak NO" ([14]). The methodology used in the development of these guidelines by the expert committee was transparent, scientifically robust and the conflicts of interests of the committee members were disclosed.

From a patient's subjective standpoint, subtle changes in FVC, as noted in phase II and III clinical trials with pirfenidone, unless associated with improved outcomes as perceived by them, such as, for instance, improvement in symptoms, quality of life, enhanced survival, may not be clinically meaningful for them. The appropriate outcome measure for phase III IPF clinical trials has been the subject of recent ongoing raging debate which we will not repeat here, other than to reiterate that while changes in FVC at 6 and 12 months have been *correlated with survival* in patients with IPF,[17] evidence to date *does not support it as a surrogate for survival*.[18–20] We believe proposed improved effects on exercise capacity and reduced exacerbations with pirfenidone treatment are not supported by the trial data.

With the exception of the first phase II clinical trial with pirfenidone, none of the subsequent clinical trials have tested the efficacy of pirfenidone for IPF patients with severe functional impairment. It was apparent that patients with IPF whose DLCO was <30% predicted, continued to deteriorate and die despite treatment with pirfenidone.[2]

WORLDWIDE DIFFERENCES IN REGULATORY APPROVAL

When trying to decide whether to fight for funding for pirfenidone for IPF patients (annual cost in the UK estimated at ~£25 000 per year), the physician and the patient is rather baffled by the different attitudes and policies of the regulatory agencies for drug approval and clinical use. Currently pirfenidone is licensed for use in IPF in Japan and the EU. The FDA in USA, upon review of the same data, rejected the license application for pirfenidone as a treatment for IPF, and another phase III trial, ASCEND, is currently under way to address its concerns. In the interim, pirfenidone is available for clinical use in India—the drug cost for a year's treatment with pirfenidone in India is ~US$500. The differences in policies by regulatory agencies for approval of pirfenidone as a treatment for patients with IPF, and the huge differences in costs in different countries and continents, have left the patient neglected and confused.

In the UK, the National Institute for Clinical Excellence (NICE) has published (at the time of writing) draft guidance that suggests that pirfenidone may slow the rate of decline in lung function owing to IPF. The NICE expert review group (ERG) expressed concerns that the patient populations in the clinical trials were not representative of the population seen in secondary care in England and Wales. It noted that few patients in the trial had the comorbidities that would normally be seen in clinical practice. The ERG also noted that general severity of IPF (according to mean baseline FVC or VC values of 73–81% across the four randomised controlled trials) was likely to be less severe in the trials than in UK clinical practice.[21]

NICE's provisional guidance is that due to uncertainties around the data for pirfenidone, and when compared with best supportive care, that treatment with pirfenidone would not represent a cost-effective treatment option for the NHS. At the time of writing, NICE draft guidance does not recommend pirfenidone treatment for patients with IPF with mild to moderate functional impairment.[21]

IS PIRFENIDONE SAFE?

Pirfenidone does have side effects, including liver dysfunction and photosensitivity. A recent study in patients treated with

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pirfenidone in the UK on the compassionate use programme demonstrated that 44% of patients had an adverse event with pirfenidone, with only half of them continuing on pirfenidone after a dose-reduction. Interestingly, 38% of the patients receiving drug in the compassionate use programme were using domiciliary oxygen which was an exclusion criteria for the CAPACITY trials, so the drug is already being used in a population of patients for which there is no evidence that it is effective.[22]

IS PIRFENIDONE COST EFFECTIVE?

The cost effectiveness of pirfenidone has never been addressed in any of the clinical trials. Draft NICE guidance suggests that pirfenidone is not cost effective for prescription in the NHS when compared with best supportive care. The treatment was not found cost effective, exceeding £30 000/QUALY, the standard threshold of cost effectiveness used by NICE.

OUR SUMMARY OF THE EFFECTIVENESS OF PIRFENIDONE AS MONOTHERAPY THERAPY IN IPF

We believe it is prudent for the physician considering pirfenidone as a treatment for the patient with IPF to be mindful of the following facts:

1. A highly selected subgroup of patients with mild to moderate functional impairment in IPF was enrolled in clinical trials of pirfenidone and, therefore, the results from these studies to date cannot be extrapolated to all patients with IPF.
2. There has been no improvement in respiratory symptoms and/or quality-of-life measurements reported with pirfenidone.
3. There is no reported decrease in mortality.
4. There are significant adverse effects associated with pirfenidone treatment—skin reaction, gastrointestinal and constitutional.
5. The uncertain clinical significance of the observed changes in FVC makes it difficult to recommend pirfenidone treatment outside further clinical trials.
6. The cost of pirfenidone is high in the European Union and Japan, where pirfenidone has been approved for treatment of IPF and is available for clinical use.
7. Cost effectiveness has not been assessed in a clinical trial, and the estimated cost per QUALY (£30 000) is deemed above the threshold for recommendation by NICE.

SOME UNANSWERED QUESTIONS

The clinical trials of pirfenidone have highlighted many drawbacks in current trial design in IPF. However, significant problems exist in assessing the response to treatment in the clinical setting for patients with IPF. How can we assess whether there is a treatment response since the effect of pirfenidone over a year on FVC is within the variability of testing of FVC measurement. There is a clear need for a reliable biomarker. The optimal duration of therapy is unknown as a biomarker (functional, molecular or otherwise) that is a surrogate for survival is yet to be determined. In the interim, do we infer from other clinical trials, such as the hypertension and cholesterol trials, that in IPF, stabilisation in FVC at the end of 1 year of treatment with an antifibrotic agent, resets the disease process, and that continuous treatment with pirfenidone is therefore justified? These and other clinically relevant questions can only be answered by further studies.

IMPROVING THE PATHWAY FOR DRUG DEVELOPMENT IN IPF?

Orphan diseases, such as IPF, are a challenge for the pharmaceutical industry to recover the huge costs of trials to get regulatory approval. We believe that a combination commercial–provider approach will advance IPF drug therapy. In this endeavour, there is a greater need for public cofunding of IPF trials, much as there has been for very successful MRC-funded leukaemia trials in the UK. This could be facilitated by the National Comprehensive Research Network to actively promote IPF studies. The recently reported TIPAC study in IPF shows that large multicentre drug trials in IPF can be conducted in the UK on a tight budget.[23] We also believe that the traditional 100% commercially driven trials development for diseases, such as IPF, discourages some pharmaceutical industries and/or companies to undertake economic risks and, thus, biologically plausible novel compounds may never be translated from the bench to the clinic. Since several cellular and molecular processes in the pathogenesis of IPF have links to cancer biology,[24] assessment of treatment response to IPF similar to assessing treatment response to cancer may yield positive results for patients with IPF.

IN SUMMARY, SHOULD PIRFENIDONE BE ROUTINELY PRESCRIBED FOR PATIENTS WITH IPF IN 2013?

It is hoped that the results of the ongoing ASCEND trial and postmarketing studies in Japan and Europe will clarify the myths from facts and ultimately determine if pirfenidone is truly beneficial to the subgroup of patients with IPF. We believe, however, that there will be no magic bullet for IPF, and that a combination approach will likely yield the needed positive results for outcome for patients with IPF. The apparent limited efficacy of pirfenidone, and the huge costs of prescribing it at this time of financial austerity, warrant further studies before routine use can be recommended. We emphasise the need for the physician confronted with this question to be well educated regarding the facts, so that when confronted by patients about pirfenidone they can adequately address their questions.

Please let us know what you think by answering our short survey monkey poll at: http://www.surveymonkey.com/s/HFLJRZK

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