The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation

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Scientific summary

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Background

Idiopathic pulmonary fibrosis (IPF) is a serious lung disease, the exact cause of which is not known. It generally affects people over 60 years of age and the main symptoms are shortness of breath and a cough, which can have a considerable impact on day-to-day life. IPF was once thought to progress at a steady, predictable rate, but it is now known that this is often not the case. Many people with IPF deteriorate rapidly, while others have periods of relative stability. In general, people with IPF survive for between 2 and 5 years. Evidence shows that the number of people with IPF is increasing, although the reasons for this are unclear. IPF is a difficult condition to manage, particularly in the later stages. Few treatments are available for IPF and none offers a cure. Treatments aim to reduce symptoms and improve survival. The type of treatment offered can vary and with a number of new treatments emerging it is timely to establish which are effective and provide the best value for money to the NHS.

Objectives

To evaluate the clinical effectiveness and cost-effectiveness of the different treatment strategies used within the NHS for IPF through systematic reviews of the evidence for clinical effectiveness, cost-effectiveness and quality of life (QoL), and economic modelling relevant to the UK setting to estimate the cost-effectiveness of the different treatments.

Methods

Search strategies were developed and applied to 11 electronic bibliographic databases (including The Cochrane Library, MEDLINE and EMBASE) from database inception to July 2013. Bibliographies of retrieved papers were screened and experts contacted to identify any additional published and unpublished references.

Titles and abstracts (where available) were screened for potential eligibility by two reviewers independently using inclusion criteria that were defined a priori. Screening of the full text of retrieved papers was performed by one reviewer and checked by a second. For the systematic review of clinical effectiveness, studies were eligible for inclusion if the participants had a confirmed diagnosis of IPF and the interventions under study were currently used to manage symptoms or modify IPF. Randomised controlled trials (RCTs) and controlled clinical trials were eligible for inclusion. Data extraction and assessment of methodological quality were undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion at each stage or consultation with a third reviewer if necessary. Data were synthesised through a narrative review with tabulation of the results of included studies. Where appropriate, the studies were combined in a meta-analysis and heterogeneity was assessed. A network meta-analysis (NMA) focusing on pharmacological treatments for IPF and assessing forced vital capacity (FVC) end points was undertaken on 10 studies. The FVC end point was measured on two continuous scales and the NMA used the standardised mean difference approach.

Systematic literature searches were undertaken to identify full economic evaluations of interventions to manage IPF, and to assess the health-related quality of life (HRQoL) of people with IPF. Studies reporting HRQoL in people with IPF were eligible for inclusion if they used either generic preference-based measures or the St George's Hospital Respiratory Questionnaire, a disease-specific instrument used in IPF.

Data were extracted in a standardised form by a health economist and checked by a systematic reviewer, with any differences resolved through discussion.

A cost–utility decision-analytic model was developed to compare the cost-effectiveness of pharmacological interventions for the treatment of IPF. The model incorporates three survival curves, which are used to inform the probabilities of transition from three health states: unprogressed IPF, progressed IPF and lung transplant. Treatment effects are obtained from NMA. Utility values are applied to the health states to estimate total quality-adjusted life-years (QALYs). Costs are included for treatments, treatment monitoring, acute exacerbations, lung transplant and adverse events. The outcome of the economic evaluation is reported as cost per QALY gained.

Results

Eight hundred and fourteen references were identified by searches for clinical effectiveness. Fourteen studies were included, of which one evaluated azathioprine, three *N*-acetylcysteine (NAC) (alone or in combination), four pirfenidone, one BIBF 1120 (nintedanib), one sildenafil, one thalidomide, two pulmonary rehabilitation, and one a disease management programme. Study quality was generally good with a low risk of bias; however, where there were areas of greater risk of bias, these have been highlighted.

In patients with mild to moderate IPF, 10 studies evaluating five pharmacological interventions (azathioprine, BIBF 1120, NAC, pirfenidone and thalidomide) were included. In a small RCT, treatment with azathioprine and prednisolone led to an improvement in survival compared with placebo and prednisolone when an age-adjusted analysis was used. There was no effect on lung function. This trial had an unclear risk of bias and it is possible that the trial included participants who would have been diagnosed with non-specific interstitial pneumonia, which may in part explain the treatment effect. Follow-up was 12 months. BIBF 1120 300 mg/day was more favourable than placebo on some measures of lung function, rates of acute exacerbations and the number of deaths; however, the primary outcome of annual rate of decline in FVC was not statistically significantly different between groups in this 54-month study. Treatment with NAC was evaluated in three studies: in combination with azathioprine and prednisolone in two and as a single agent in an inhaled format in one. Follow-up was approximately 12 months in these studies. Study results were mixed, with no benefit from triple therapy on FVC compared with placebo in one study; however, there was a benefit on vital capacity when compared with double therapy in another study. Inhaled single-therapy NAC did not have a statistically significant effect compared with a control. Secondary outcomes were reported, similarly with mixed results across the three studies. The two studies with triple-therapy interventions had a low risk of bias; however, the study using nebulised NAC had an unclear risk of bias. Pirfenidone was studied in four RCTs, and meta-analysis of FVC shows that pirfenidone appears to demonstrate an effect when compared with placebo treatment. However, caution is required in interpreting these data as the outcomes pooled were different, and as a consequence a standardised mean difference analysis was undertaken; in addition, the timing of assessment of these outcomes varied (from 48 weeks to 72 weeks). Results for secondary outcomes were generally seen to be less favourable to pirfenidone. In a small crossover study, thalidomide appeared to improve cough, cough-related quality life and respiratory-related QoL, compared with treatment with placebo.

One study assessed sildenafil for those with moderate to severe IPF; the participants in this study also had evidence of pulmonary hypertension. Results on the primary outcome, a 20% improvement on the 6-minute walk test, were not statistically significant between the sildenafil and placebo groups. Results for secondary outcomes were mixed, with some favourable to sildenafil and others favouring placebo. This study followed participants for 12 weeks.

Adverse events from the pharmacological interventions were generally mild to moderate and were reasonably well balanced between the treatments and the placebo arms across the studies, with the

exception of thalidomide. Severe adverse events appeared to be more common in one study in those treated with triple therapy.

Three studies evaluated non-pharmacological treatments for populations with IPF. Two compared pulmonary rehabilitation with a control; the other compared a disease-management approach with a control. Results are uncertain with regard to pulmonary rehabilitation as differences favouring the intervention were seen for some outcomes but not others. The included studies had an uncertain risk of bias and outcomes were assessed at 10 and 12 weeks in the two trials, respectively, immediately after the cessation of the intervention. The third study reported limited evidence on the effects of a disease-management programme in IPF: there were no statistically significant differences in dyspnoea, and QoL results were mixed. This study has an uncertain risk of bias and follow-up was at 6 weeks, immediately after the programme had completed.

The fixed-effects NMA found only BIBF 1120 and pirfenidone to have a statistically significant improvement in FVC over placebo. A head-to-head comparison of BIBF 1120 versus pirfenidone showed a trend favouring BIBF, but this was not statistically significant. Caution is required in the interpretation of the results of the NMA.

One full economic evaluation of treatment for patients with IPF was identified. This examined the benefits of a testing strategy prior to treatment with NAC triple therapy but did not examine the cost-effectiveness of IPF treatment. The systematic review of QoL studies included 23 studies; results varied, but generally appeared to show that IPF has an adverse effect on HRQoL compared with population norms, and that HRQoL is likely be diminish as IPF becomes more severe.

The model base-case results show increased survival for five of the treatments compared with best supportive care (BSC), at increased cost. Only one treatment, inhaled NAC, is cost-effective at a willingness-to-pay (WTP) threshold of £30,000, but its treatment effect does not achieve statistical significance in either the single primary study or the NMA. The treatment effect of inhaled NAC compared with BSC is associated with an expected value of partial perfect information of £15.8M at a WTP threshold of £20,000.

Discussion and limitations

This evidence synthesis reports the clinical effectiveness and cost-effectiveness of a range of interventions which are currently used, or proposed to be used, to manage IPF in the UK. No previous systematic reviews have included all potentially relevant treatments for IPF, and there have been only limited economic evaluations in this area. The results of this report complement recent national guidance in the UK. The current evidence suggests that there are few treatments that have any effect on surrogate outcomes which can be linked through evidence to patient-related outcomes such as mortality. There is a scarcity of studies on interventions in symptom management and palliative care in IPF.

This evidence synthesis has been undertaken following the principles for conducting systematic reviews and economic evaluations. Limitations to this evidence synthesis include there being few direct comparisons of treatments identified. An indirect comparison through a NMA was performed; however, caution is recommended in the interpretation of these results. In relation to the economic model, there is an assumption that pharmacological treatments have a constant effect on the relative rate of FVC percentage decline.

Research is required into the effects of symptom control interventions, in particular pulmonary rehabilitation and thalidomide. Other research priorities include a well-conducted RCT on inhaled NAC therapy and an updated evidence synthesis once the results of ongoing studies are reported.

Conclusions

This evidence synthesis has identified limited evidence of the effectiveness of a number of available treatments for IPF. Pirfenidone and BIBF 1120 appear to be clinically effective; however, general recommendations cannot be made in terms of their cost-effectiveness owing to limitations in the evidence base. Further research is required in a number of areas as outlined above.

Study registration

This study is registered as PROSPERO CRD42012002116.

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