Anti-reflux therapy in idiopathic pulmonary fibrosis

This background document provides further information to support applicants for this call. It is intended to summarize what prompted the call and the existing evidence base, including relevant work from the HTA and wider NIHR research portfolio. It was researched and written on the basis of information from a search of relevant sources and databases, and in consultation with a number of experts in the field. Searches and information provided were up to date as of December 2017.

Source of topic

Patient group
Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic interstitial lung disease (ILD) of unknown origin. It is a difficult disease to diagnose and often requires the collaborative expertise of a chest physician, radiologist and histopathologist to reach a consensus diagnosis. Most people with IPF experience symptoms of breathlessness, which may initially be only on exertion. Cough, with or without sputum is a common symptom. Over time, these symptoms are associated with a decline in lung function, reduced quality of life and ultimately death. [NICE]

The incidence of IPF is approximately 8 to 9 per 100,000 person years, which means more than 5000 new cases occur in the UK each year. It is rare in people younger than 45 and the median age of presentation is 70 years. The prevalence is around 15 to 25 per 100,000 and increases with age. The majority of people with IPF are ex-smokers and IPF often co-exists with chronic obstructive pulmonary disease (COPD). The median survival for people with IPF in the UK is approximately 3 years from the time of diagnosis, but it is recognised that there is a very wide spectrum associated with survival. However, approximately 20% of patients survive for greater than 5 years. [NICE]

Patients with IPF have frequent comorbid conditions, including a high reported prevalence of gastro-oesophageal reflux (GER) and gastrooesophageal reflux disease (GERD) [1]. The potential role of GER in the pathogenesis or progression of IPF has been an important focus of research, in an effort to find effective therapeutic approaches to patient management. GER and consequent microaspirations have been proposed as pathogenic in IPF but there is conflicting data on whether anti-reflux therapy might confer clinical benefit in terms of slowing chronic disease progression, and possibly even survival. [1]

NICE and other guidance

Disease-modifying pharmacological interventions
There is no conclusive evidence to support the use of any drugs to increase the survival of people with idiopathic pulmonary fibrosis.

1.5.11 For guidance on pirfenidone, see the NICE technology appraisal on pirfenidone for the treatment of idiopathic pulmonary fibrosis. For guidance on nintedanib, see the NICE technology appraisal on nintedanib for the treatment of idiopathic pulmonary fibrosis.
1.5.12 Do not use any of the drugs below, either alone or in combination, to modify disease progression in idiopathic pulmonary fibrosis:

- ambrisentan
- azathioprine
- bosentan
- co-trimoxazole
- mycophenolate mofetil
- prednisolone
- sildenafil
- warfarin.

1.5.13 Advise the person that oral N-acetylcysteine is used for managing idiopathic pulmonary fibrosis, but its benefits are uncertain.

1.5.14 If people with idiopathic pulmonary fibrosis are already using prednisolone or azathioprine, discuss the potential risks and benefits of discontinuing, continuing or altering therapy.

1.5.15 Manage any comorbidities according to best practice. For gastro-oesophageal reflux disease, see Managing dyspepsia in adults in primary care (NICE clinical guideline 17).

- NICE Quality standard [QS79] Idiopathic pulmonary fibrosis in adults (Jan 2015) includes quality statements about the assessment for home and ambulatory oxygen therapy and pulmonary rehabilitation but doesn’t include any quality statements that are relevant to the present topic.


  **Recommendation:** We suggest that clinicians use regular antacid treatment for patients with IPF (conditional recommendation, very low confidence in estimates of effect).

  The guideline also notes these further research opportunities: Further RCTs are needed to compare antacid treatment versus placebo in patients with IPF. Also, further research should focus on the drug interaction of PPIs with other IPF medical treatment, the long-term safety of PPI treatment for patients with IPF with or without symptoms of gastroesophageal reflux/disease (GER/GERD), the role of therapy in nonacid reflux, and the role of abnormal GER and microaspiration in the pathogenesis, progression, and/or exacerbation of IPF. Further studies are warranted to determine safety and efficacy of decreasing risks for GER and microaspiration by surgical interventions in patients with IPF.


  There is conflicting evidence regarding the role of antacid therapy in IPF. Only observational data exist, with some studies suggesting benefit, some suggesting no benefit and one suggesting potential for harm. Since appropriately designed studies assessing the roles of medical or surgical treatment of gastro-oesophageal reflux in IPF are awaited, it remains unclear whether these treatment strategies confer benefit.

**Current practice and proposed intervention**

NICE acknowledges that some drugs once widely used to treat IPF may in fact have been harmful but we have only learned this by performing rigorous clinical trials. The limitations of current pharmacological therapies for IPF highlight the importance of other forms of treatment including lung transplantation and best supportive care such as oxygen therapy, pulmonary rehabilitation and palliation of symptoms but the overall evidence for any intervention is not high quality. There is no conclusive evidence to support the use of any drugs to increase the survival of people with idiopathic pulmonary fibrosis. [NICE]

As noted above GER is a common co-morbidity and has been implicated in the pathogenesis and progression of IPF but the quality of available evidence is very low. Only with a high quality randomised
trial will the potential therapeutic role of anti-reflux therapy, and PPIs in particular, be confirmed or refuted.

Completed research

Evidence Synthesis

To determine the effects of ambulatory and short-burst oxygen therapy, separately, on exercise capacity, dyspnoea and quality of life in people with ILD and particularly those with IPF. Searches to May 2016 identified just 3 studies with 98 participants which met inclusion criteria. As such there was not enough evidence to support or refute the use of ambulatory or short burst oxygen in ILD due to the limited number of included studies and data.

To determine whether pulmonary rehabilitation in patients with ILD has beneficial effects on exercise capacity, symptoms, quality of life and survival compared with no pulmonary rehabilitation in patients with ILD. Searches to June 2014 identified 9 studies which met inclusion criteria with 5 studies (160 patients) included in a meta-analysis. The authors concluded that pulmonary rehabilitation seems to be safe and lead to short term improvements in lung function outcomes but the evidence is of low to moderate quality and there is little evidence of longer-term effects.

There are also older Cochrane reviews on non-steroid agents for IPF (2010) [6] and corticosteroids for IPF (2003) [7] but these are now out of date and have been updated via the broader HTA funded evidence synthesis detailed below by Loveman et al in 2015.

There are also a number of excellent recent narrative reviews which provide useful background and context about IPF and it’s management more generally as well as considering the impact of reflux [8,1]. Both reviews also highlight some of the other studies which have been conducted which did not meet inclusion criteria for the evidence syntheses.

Primary Research

Post-hoc analysis of CT images from a US atherosclerosis cohort study (about 6,000 patients) with the collected images allowing evaluation for subclinical ILD. The researchers compared analysed use of reflux drugs (PPIs and histamine-2-receptor blockers (H2B)). PPI but not H2B use was associated with fewer areas of lung damage on CT in asymptomatic adults suggesting that PPI might confer some protection against ILD/IPF development/progression.

Post-hoc analysis from the placebo arm of three trials in IPF and comparing outcomes between groups who were and were not prescribed anti-reflux therapies (about 600 patients in total). This analysis showed no benefit from such therapy and might potentially be associated with an increased risk of infection in those with advanced disease.

However, Rahgu 2016 [11] questions these studies and notes that the results from all the posthoc, subgroup, and exploratory analyses must be interpreted with great caution and the data generated from such analyses must always be considered at best as hypothesis-generating. Only well designed randomised trials can answer the specific questions regarding the safety and efficacy of antacid therapy in patients with IPF.

Small (27 patients) retrospective single-centre study of IPF patients with worsening symptoms and pulmonary function despite antacid treatment for abnormal reflux who underwent laparoscopic anti-reflux surgery. There was a possible trend towards stabilisation in observed FVC.

Research in progress

Evidence Synthesis


- Bajwah et al. Pharmacological and non-pharmacological interventions to improve symptom control and quality of life in patients with interstitial lung disease: a systematic review. PROSPERO 2017: CRD42017065933. Given the lack of evidence in previous reviews this is unlikely to identify anything new/significant.

- Scott et al. Comparing treatments for idiopathic pulmonary fibrosis: a systematic overview of published network meta-analyses. PROSPERO 2017: CRD42017072876. Given the lack of evidence in previous reviews this is unlikely to identify anything new/significant.


Primary Research

There are numerous ongoing studies looking at various different management options for IPF but only a couple specifically related to anti-reflux therapy were identified.

- **NCT0198296**: Treatment of IPF With Laparoscopic Anti-Reflux Surgery (WRAP-IPF). RCT. N = 58, active and was due to complete Nov 2017. USA. 
  
  *Inclusion criteria:* i) confirmed diagnosis of idiopathic pulmonary fibrosis, ii) abnormal GER on 24-hour pH monitoring (DeMeester score > 14.7), iii) able to provide informed consent, iv) willing to undergo laparoscopic anti-reflux surgery.

  *Primary outcome:* decline in forced vital capacity (FVC) at 48 weeks.

- **NCT02085018**: Pilot Trial Of Omeprazole in Idiopathic Pulmonary Fibrosis (IPF). RCT. N = 60. Recently completed and results expected to be published soon. UK. 
  
  *Inclusion criteria:* i) IPF is considered the most likely diagnosis by the Regional Interstitial Lung Disease Multidisciplinary Team meeting (ILD-MDT), ii) History of cough, with or without exertional dyspnoea, iii) High resolution computed tomography (HRCT) scan features of honeycombing in a predominantly basal subpleural distribution, iv) Bibasal crackles on auscultation, v) Features of a restrictive ventilatory defect [vital capacity (VC) <90% predicted and/or diffusion factor for carbon monoxide (Tco) <90% predicted], vi) Aged 40-85 years, vii) Patients taking short courses (eg. 2 months) of proton pump inhibitors (PPI) will be eligible once the treatment has been discontinued for a minimum of 1 month.

  *Primary outcome:* objectively measured cough frequency at 90 days.

NETS research

The NETS programmes have funded a number of studies in IPF and/or ILD but nothing which directly overlaps with or causes concern for the proposed research:

- **HTA evidence synthesis 10/50/06**: Treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. Dr Emma Loveman, University of Southampton. Published March 2015. Conclusions: Few interventions have any statistically significant effect on IPF and a lack of studies on palliative care approaches was identified. No relevant trials of anti-reflux therapy were included.

- **HTA primary research 12/01/04**: A randomised, placebo controlled trial of extra-oesophageal reflux treatment in the management of upper respiratory symptoms. [TOPPITS: Trial of Proton Pump
Inhibitors in Throat Symptoms]. Professor Janet Wilson, University of Newcastle upon Tyne. Active and due to complete June 2018.

- EME primary research 12/206/09: The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary fibrosis with the Addition of Co-trimoxazole (EME-TIPAC). Professor Andrew Wilson, University of East Anglia. Active and due to complete Nov 2018.


References