

The Treatment of Idiopathic Pulmonary Fibrosis: an unmet clinical need

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ABSTRACT

Idiopathic Pulmonary Fibrosis (IPF) is a progressive lung condition with no clear underlying definitive cause. This article will discuss previous landmark studies in IPF and review current and potential future treatment options.

Key Words: Idiopathic pulmonary fibrosis; respiratory medicine; restrictive lung disease

Introduction

Whilst many causes of pulmonary fibrosis can be identified and treated, including sarcoidosis, hypersensitivity pneumonitis such as bird-fanciers' lung and drug induced causes including methotrexate, bleomycin and nitrofurantoin, the management of idiopathic pulmonary fibrosis (IPF) is largely palliative, with no proven effective therapy.

IPF describes a progressive condition of characteristic clinical symptoms and signs including breathlessness and fine basal inspiratory crackles (90% of cases) and the presence of finger clubbing (49-66% of cases).^{1,2} In addition to these findings, in IPF patients, upon lung biopsy pathological evidence of usual interstitial pneumonia (UIP) can be found in addition to the characteristic HRCT appearance of bibasal sub pleural reticular opacities with honeycombing.³ Other interstitial lung diseases can present with clinical and radiological features very similar to IPF, notably non-specific interstitial pneumonia (NSIP). However distinguishing IPF from other similar conditions is important given that the 5 year-survival in IPF is usually <20%, compared to >50% for NSIP.³ Accurate diagnose of IPF requires integration of clinical radiological and where available histological data in a multi-disciplinary setting.

This article will review the previous and current management strategies of IPF and discuss potential future treatment options.

Clinical Case

Mr HS is a 60 year-old-man and presented to the respiratory outpatient clinic with a 14 months history of worsening shortness of breath. Mr HS described how his breathlessness was worse on exertion and was associated with a dry cough. Mr HS has never smoked and works as a school-teacher. He has a history of hypertension and hypercholesterolaemia and has a family history of ischaemic heart disease. He has no history of asbestos exposure and does not have any pets. He lives at home with his wife, who is in good health. He takes ramipril and simvastatin. On examination Mr HS has evidence of finger clubbing. Bibasal crackles were heard on chest auscultation.

Chest radiography was abnormal with bi-basal fine reticular shadowing and HRCT showed established pulmonary fibrosis with honeycombing (see figure 1). Spirometry showed a restrictive pattern with a reduced carbon monoxide transfer factor (TLCO).

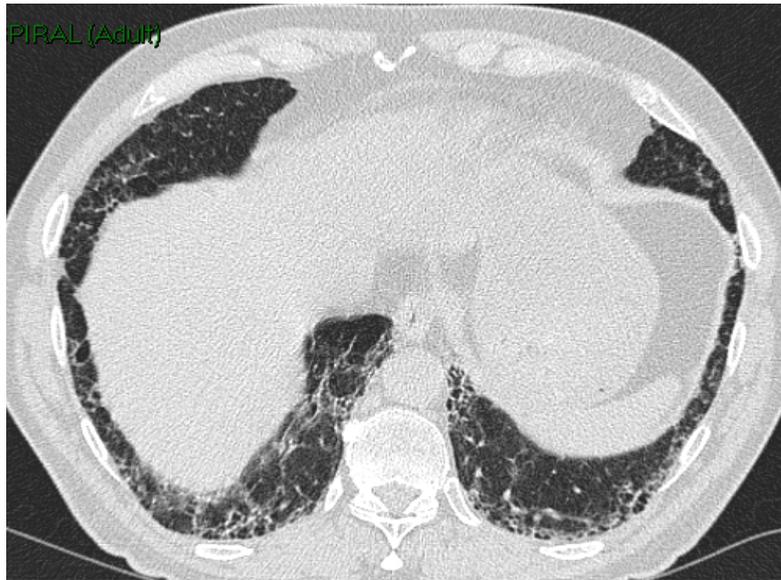


Fig 1. HRCT showing peripheral honeycomb appearance consistent with IPF.

Mr HS underwent a surgical lung biopsy that showed a usual interstitial pneumonia pattern of disease. In view of the clinical history and radiological and pathological investigations a diagnosis idiopathic pulmonary fibrosis was made.

Mr HS has asked about possible treatment options and the evidence for each. The most relevant drugs that may be applicable in this setting are discussed below.

Drug Therapy

N-acetylcysteine, Azathioprine and Prednisolone Therapy

Historically corticosteroids, often at high dose (e.g. prednisolone 60mg/day or higher) were given alone for the treatment of IPF due to largely observational studies reporting subjective improvements in patient outcome. However there are no randomised controlled studies which directly support the use of corticosteroid monotherapy in IPF and as a result a Cochrane Review concluded that there was no evidence for this approach.⁴

Several randomised controlled trials have however focussed upon the use of corticosteroids as an adjunct to immunosuppressive therapy in IPF patients. Raghu et al performed a clinical trial, where 27 patients with IPF were randomised to either prednisolone with azathioprine versus prednisolone alone.⁵ In this small study, a survival benefit was seen with the prednisolone with azathioprine group in comparison with prednisolone alone. However there was no significant difference between survival until after 9 years follow up. As we know that the median survival of IPF is approximately 3 years,⁶ it is unclear whether the patients in the study had typical IPF by current diagnostic criteria. In addition, there was no placebo group in this study, and indeed there are no randomised controlled trials that compare corticosteroids and immunosuppressive therapy versus placebo. Despite these shortcomings, for the subsequent 15 years at least, prednisolone and azathioprine was advocated as a reasonable, but unproven treatment strategy for IPF.

N-acetylcysteine (NAC) is the derivative of the amino acid L-cysteine and is the precursor in the formation of the anti-oxidant glutathione. Glutathione deficiency has been found in patients with IPF.⁷ With these observations studies began to focus upon the use of N-acetylcysteine in the treatment of IPF,⁸ and culminated in a large phase 3 trial in IPF patients. The INFIGENIA study was a double-blind controlled trial where each patient received prednisolone and azathioprine and were then randomised to receive NAC or

matched placebo⁹. In 155 patients, with radiological imaging consistent with IPF, the use of NAC was associated with a preservation of lung function. Whilst neither treatment regimes halted a decline in lung function, forced vital capacity (FVC) and transfer factor (DLCO) were 9% and 24% greater in the NAC group after 1 year follow up. Although this study did not compare NAC versus placebo alone, these findings resulted in a treatment regime of prednisolone, azathioprine and NAC being considered by some clinicians as “standard treatment” for patients with IPF, effectively replacing the previously considered ‘standard’ of prednisolone and azathioprine. Since there was no true placebo group (i.e. patients that did not receive any active drug) it cannot be determined whether there were actually any beneficial effects with NAC in IPF or whether NAC simply reduced the potential side effects attributable to prednisolone and azathioprine.¹⁰

In order to partially address the unanswered questions raised by the INFIGENIA study, the PANTHER study, was designed to assess whether there were any benefits with NAC, prednisolone and azathioprine treatment versus no therapeutic treatment.¹¹ As of October 2011, PANTHER had enrolled 238 out of the 390 expected participants. The three treatment limbs within the study were NAC, prednisolone and azathioprine versus NAC alone versus placebo. Interim data released by the National Heart Lung and Blood Institute, found that participants treated with NAC, prednisolone and azathioprine had increased mortality (11% versus 1% in placebo limb), serious adverse events (31% versus 9% in placebo limb) without any evidence of therapeutic benefit.¹² Due to these findings the treatment limb including NAC, prednisolone and azathioprine was stopped. No safety issues identified with participants with the NAC treatment limb and as a result the study has been continued comparing NAC alone versus placebo. This will help us to determine whether or not NAC monotherapy has any benefit in IPF for the treatment of IPF.

These interim findings of the PANTHER study highlight the fundamental importance of performing placebo-controlled trials in IPF. Understandably when “standard” therapies have been established with or without an evidence base, it can be ethically challenging to perform clinical trials including placebo limbs as these are seen to be denying participants putatively beneficial treatments. Pending the final outcome of the PANTHER study, international guidelines do not recommend the use of NAC, prednisolone or azathioprine, as monotherapy or combined therapy, for the majority of patients with IPF.¹³

Pirfenidone

Pirfenidone is a pyridone compound that has been investigated as a therapy for IPF. Pirfenidone has been shown to inhibit fibroblast proliferation and collagen synthesis *in vitro*,^{14,15} and has also been shown to ameliorate bleomycin induced pulmonary fibrosis in murine models.^{16,17} Whilst both open-labelled and placebo controlled studies have been performed looking at the potential benefits of pirfenidone, the impact of these studies was limited due to issues including small sample size, premature trial termination and change of primary endpoint.¹⁸⁻²⁰ The CAPACITY programme, included 2 concurrent phase 3 multi-centre randomised controlled trials investigating the role of pirfenidone in patients with mild-to-moderate IPF.²¹ Patients were randomised to either pirfenidone or matched placebo for 72 weeks. In study 004, 174 patients were assigned to high dose pirfenidone, 87 to low dose pirfenidone and 174 to placebo. In study 006, 171 patients were assigned to the same high dose of pirfenidone used in study 004 and 173 to placebo.

The primary endpoint for the CAPACITY programme, in common with most recent studies in IPF, was based upon measures of lung function with the change in FVC % predicted at 72 weeks being used in each case. Despite the same endpoint being used for both studies the results were conflicting. In study 004, high-dose pirfenidone significantly reduced the

decline in percentage predicted FVC with an effect size of 4.4% at week 72; but in study 006, there was no difference between the groups in the primary endpoint at week 72. However, in study 006 a consistent pirfenidone treatment effect was found up to week 48. When the results of both studies were pooled together, significant improvements were found with pirfenidone treatment in both lung function and exercise tolerance. These findings led the authors to conclude that pirfenidone was an appropriate treatment option for patients with IPF. At present the potential use of pirfenidone for the treatment of IPF in the United Kingdom is being reviewed and evaluated by the National Institute of Clinical Excellence (NICE).²²

Alternatives to Drug Therapy

Lung Transplantation and Best Supportive Care

Lung transplantation has the potential to significantly improve survival in selected patients with IPF. However, the risks of transplantation rise considerably in patients over the age of 60 yrs. Since the median age of presentation in IPF is around 70 yrs, only a small fraction of patients will be eligible for transplantation. Younger patients with IPF who are deemed suitable for lung transplantation should be referred to a transplant centre if the disease is advanced or progressive based upon changes in lung function following serial monitoring.³ The estimated 5-year survival post-transplant is encouraging at 50-56%.^{23,24}

For the vast majority of patients in whom lung transplantation is not an option, best supportive care remains the cornerstone of IPF management. Best supportive care involves managing patients' symptoms and includes the use of oxygen therapy, pulmonary rehabilitation, prescription of analgesics/anxiolytics and close monitoring thereby achieving early recognition of terminal decline and liaison with palliative care specialists when appropriate.³

Summary

There is no doubt that an effective treatment for idiopathic pulmonary fibrosis is urgently needed. Whilst previous treatments have in part been based upon small studies and observational work, the importance of placebo-controlled trials is clearly seen within the evolution of potential treatments for IPF. Whilst some medical therapies offer promise to the management of IPF at present the management of patients with idiopathic pulmonary fibrosis is extremely challenging. When dealing with patients who are aware they have a progressive disease, the lack of curative treatment, results in patient care being focused upon symptom control and maintaining quality of life. Whilst lung transplantation can be considered for the minority, for the majority, enabling best supportive care and recruitment to high quality clinical trials, ideally coordinated through specialist IPF clinics, remains the best treatment option.

References

1. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. *Thorax* 1980;**35**:171-80.
2. Johnston ID, Prescott RJ, Chalmers JC, Rudd RM. British Thoracic Society study of cryptogenic fibrosing alveolitis: current presentation and initial management. *Fibrosing Alveolitis Subcommittee of the Research Committee of the British Thoracic Society. Thorax* 1997;**52**:38-44.
3. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;**63** Suppl 5:v1-58.
4. Richeldi L, Davies HR, Ferrara G, Franco F. Corticosteroids for idiopathic pulmonary fibrosis. *Cochrane Database Syst Rev* 2003:CD002880.

5. Raghu G, Depaso WJ, Cain K, et al. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991;144:291-6.
6. Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. *Chest* 1998;113:396-400.
7. Cantin AM, Hubbard RC, Crystal RG. Glutathione deficiency in the epithelial lining fluid of the lower respiratory tract in idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1989;139:370-2.
8. Behr J, Maier K, Degenkolb B, Krombach F, Vogelmeier C. Antioxidative and clinical effects of high-dose N-acetylcysteine in fibrosing alveolitis. Adjunctive therapy to maintenance immunosuppression. *Am J Respir Crit Care Med* 1997;156:1897-901.
9. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005;353:2229-42.
10. Hunninghake GW. Antioxidant therapy for idiopathic pulmonary fibrosis. *N Engl J Med* 2005;353:2285-7.
11. McGrath EE, Millar AB. Hot off the breath: triple therapy for idiopathic pulmonary fibrosis--hear the PANTHER roar. *Thorax* 2012;67:97-8.
12. <http://www.nhlbi.nih.gov/new/pantherQA.htm> (Accessed 02/05/2012)
13. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788-824.
14. Hirano A, Kanehiro A, Ono K, et al. Pirfenidone modulates airway responsiveness, inflammation, and remodeling after repeated challenge. *Am J Respir Cell Mol Biol* 2006;35:366-77.
15. Nakazato H, Oku H, Yamane S, Tsuruta Y, Suzuki R. A novel anti-fibrotic agent pirfenidone suppresses tumor necrosis factor-alpha at the translational level. *Eur J Pharmacol* 2002;446:177-85.
16. Oku H, Nakazato H, Horikawa T, Tsuruta Y, Suzuki R. Pirfenidone suppresses tumor necrosis factor-alpha, enhances interleukin-10 and protects mice from endotoxic shock. *Eur J Pharmacol* 2002;446:167-76.
17. Iyer SN, Wild JS, Schiedt MJ, Hyde DM, Margolin SB, Giri SN. Dietary intake of pirfenidone ameliorates bleomycin-induced lung fibrosis in hamsters. *J Lab Clin Med* 1995;125:779-85.
18. Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. *Am J Respir Crit Care Med* 1999;159:1061-9.
19. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;35:821-9.
20. Collard HR. Idiopathic pulmonary fibrosis and pirfenidone. *Eur Respir J* 2010;35:728-9.
21. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011;377:1760-9.
22. <http://guidance.nice.org.uk/index.jsp?action=byID&o=13039> (Accessed 02/05/2012)
23. Mason DP, Brizzio ME, Alster JM, et al. Lung transplantation for idiopathic pulmonary fibrosis. *Ann Thorac Surg* 2007;84:1121-8.
24. Keating D, Levvey B, Kotsimbos T, et al. Lung transplantation in pulmonary fibrosis: challenging early outcomes counterbalanced by surprisingly good outcomes beyond 15 years. *Transplant Proc* 2009;41:289-91.