Commentary

# Anti-cytokine therapy in fibrosing alveolitis: where are we now?

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## Abstract

Idiopathic pulmonary fibrosis (IPF) is a condition that has a poor prognosis, with a median survival of 4–5 years irrespective of treatment. Ziesche *et al* (*N Engl J Med* 1999, **341**: 1264–1269) describe an open randomised trial of 18 patients with IPF, unresponsive to corticosteroid treatment at high dose. Nine patients were treated with continued corticosteroid and nine with prednisolone plus interferon-γ 1b (IFN-γ). Significant benefits in physiological parameters are reported in the IFN-γ-treated group. An analysis of lung tissue by reverse-transcriptase-mediated polymerase chain reaction showed corresponding decreases in the transcription of transforming growth factor-β1 and connective tissue growth factor. This is the first report of treatment showing efficacy in this disease, albeit in a very preliminary study, but the data should be viewed with caution. This study is discussed in the context of other published studies of treatment for IPF and the scientific rationale on which it was based.

**Keywords:** cytokines, idiopathic pulmonary fibrosis, treatment

Idiopathic pulmonary fibrosis (IPF) is a chronic debilitating illness that leads inexorably to respiratory failure and death in most patients [1]. The 5-year mortality approaches 50% in most studies [2]. The efficacy of any treatment is questionable and this can lead to a rather nihilistic approach. Received wisdom suggests that this is a rare disease occurring mainly in elderly men and for which currently available treatment is often ineffective and can induce side effects that are worse than the condition itself. The symptoms of gradually increasing breathlessness are non-specific and often attributed to 'old age', leading to presentation at a point that can be late in the natural history of the condition. Current therapy is usually corticosteroids with or without some form of immunosuppressant. However, the data upon which this is based are limited. The fact that these treatments are still widely used reflects the difficulty of a palliative approach for clinicians and patients in such a distressing condition.

The available studies of treatment for IPF are in small numbers of patients and are rarely controlled trials [3–14]. On reviewing these studies, it is apparent that some of the patients had collagen vascular disease and therefore did not have IPF. A significant number of the responders were

CTGF = connective tissue growth factor; IFN-γ = interferon-γ 1b; IPF = idiopathic pulmonary fibrosis; NSIP = non-specific interstitial pneumonia; $PaO_2$ = partial pressure of arterial oxygen; TGF-β = transforming growth factor-β; TLC = total lung capacity; UIP = usual interstitial pneumonia.

less than 50 years old and were female, which is atypical. Histological data on these subjects were limited. The recent reclassification of interstitial lung diseases by histological features has shown a clear association between subtypes and response to treatment. Usual interstitial pneumonia (UIP) is the histological pattern that identifies IPF with little response to treatment [15,16]. Overall, these data suggest that those patients who responded to treatment in a previous trial might have had non-specific interstitial pneumonia (NSIP) rather than UIP. This exemplifies problems in the design and practice of appropriate trials in IPF owing to the relative rarity of the disease, the difficulties of including placebo controls, and the numbers of patients required to detect objective improvements.

Treatment with corticosteroids and immunosuppresive therapy is based on the concept that IPF is due to abnormalities in the immunoregulatory response, leading to progressive fibrosis rather than healing and resolution. These therapies have not been targeted at fibrogenic factors. There is a significant literature on the potential role of the fibrogenic factors transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF) in IPF [17,18]. It has also been demonstrated *in vitro* that several agents, including pirfenidone (5-methyl-1-phenyl-2-(1*H*)-pyridone) and IFN-γ, decreases their production [19,20]. The use of these agents in therapeutic trials in IPF is an exciting prospect because potentially they are affecting fibrogenesis, which can be considered a downstream aspect in the pathogenesis of IPF, a common point for clinical presentation.

One study has previously reported on the anti-fibrotic agent pirfenidone in patients with IPF [21]. This showed some limited improvement and was performed in patients with advanced diseases. Ziesche *et al* [22] have reported an open clinical trial of IFN-γ in patients with IPF. Patients were excluded if they had a total lung capacity [TLC] of less than 45% of predicted and were regarded as end stage. Patients were considered eligible if they showed no response to corticosteroid at high dose (50 mg daily for 4 weeks), with response defined as an improvement in TLC of 10%. Eighteen subjects were recruited, nine were treated with prednisolone at low dose (7.5 mg/day) and compared with nine treated with IFN-γ (200 μg, three times daily) and prednisolone (7.5 mg/week). Significant changes were reported in the IFN-γ-treated group after 12 months. Three physiological endpoints were described. Total lung capacity had decreased by 4% in the control group (from 66 ± 8% to 62 ± 6% of predicted) compared with an increase of 9% in the IFN-γ group (70 ± 10% to 79 ± 12% of predicted). The resting partial pressure of arterial oxygen ($PaO_2$) decreased in the control group from 65 ± 6 to 62 ± 4 mmHg compared with an increase in the IFN-γ group from 64 ± 9 to 76 ± 8 mmHg, with comparable improvements in post-exercise $PaO_2$. No data were reported on cigarette smoking, which is known to have an effect on outcome [23].

Transcriptional changes in TGF-$\beta_1$ and CTGF, measured by semiquantitative RT–PCR (reverse-transcriptase-mediated polymerase chain reaction), were also demonstrated in the IFN-γ group. These data permit speculation on the mechanisms responsible for these documented improvements. These data are promising but must be treated with caution [24]. The patients studied were identified by clinical, radiographic (including high-resolution computed tomography), physiological parameters and histological data. Fifteen had undergone open lung biopsy and three had undergone transbronchial biopsy; IPF was diagnosed on the basis of the presence of subpleural and periacinar fibrotic lesions with minor cellular infiltration. The recent histological reclassification of IPF shows a very significant relationship between subtype and both mortality and response to treatment, as mentioned previously [15]. The data would be significantly strengthened if the authors now had a histological review by an independent pathological expert. In addition to these histological criteria, the patients had to have shown a deterioration of a minimum of 10% decrease in lung function in the preceding 12 months despite treatment with corticosteroid and/or immunosuppressive agents for at least 6 of the preceding 12 months. The patients had a mean age of 61 years, which is young for this disease. At the start of the study the mean values of TLC were 66 ± 6% and 70 ± 10% of predicted in the two groups, which is a level that is rarely seen in the outpatient setting in the UK. An increase of 10% or 200 ml in TLC is required for an improvement to be considered significant. The authors have replied to comments on this issue, pointing out that in view of the relatively well preserved TLC in their subjects there was a mean increase of approximately 50 ml in their subjects [25]. The figures for gas transfer are not given, which is an important physiological measure that is regarded by some authorities as the most crucial in monitoring. $PaO_2$ values before and after maximal exercise were used as surrogate markers of gas exchange; however, no details of the exercise performed are given, so corrections for work performed cannot be made. Furthermore the 5-year mortality for this disease is in the region of 50%, but there were no deaths in the 18 patients despite a total of seven patients requiring oxygen therapy. The patients described in this study are unusual in their 'physiological health' at the entry to the study and lack of deterioration in the course of the study. This leads to a question of whether their apparent response to IFN-γ can be considered representative of IPF, in particular of the UIP subset, by contrast with those with the more responsive NSIP subset. Further studies of this agent are warranted but the problem of patient selection for studies of IPF remains unresolved: on the one hand, the stricter the criteria the more difficult recruitment becomes; on the other hand is the large number required to detect significant clinical outcomes.

This study gives us a glimmer of hope, firstly to raise the profile of IPF as a disease requiring more and very well designed clinical trials, and secondly as the second study to look at agents that are potentially antifibrotic, targeting the process that leads to the disability of IPF.

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