Interferon gamma-1b therapy for cryptogenic fibrosing alveolitis

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Introductory article

A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis

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Background. Patients with idiopathic pulmonary fibrosis have progressive scarring of the lung and usually die within four to five years after symptoms develop. Treatment with oral glucocorticoids is often ineffective. We conducted an open, randomized trial of treatment with a combination of interferon gamma-1b, which has antifibrotic properties, and an oral glucocorticoid. **Methods.** We studied 18 patients with idiopathic pulmonary fibrosis who had not had responses to glucocorticoids or other immunosuppressive agents. Nine patients were treated for 12 months with oral prednisolone alone (7.5 mg daily, which could be increased to 25 to 50 mg daily), and nine with a combination of 200 µg of interferon gamma-1b (given three times per week subcutaneously) and 7.5 mg of prednisolone (given once a day). **Results.** All the patients completed the study. Lung function deteriorated in all nine patients in the group given prednisolone alone: total lung capacity decreased from a mean ($\pm$ SD) of 66 ± 8 percent of the predicted value at base line to 62 ± 6 percent at 12 months. In contrast, in the group receiving interferon gamma-1b plus prednisolone, total lung capacity increased (from 70 ± 6 percent of the predicted value at base line to 79 ± 12 percent at 12 months, $p < 0.001$ for the difference between the groups). In the group that received interferon gamma-1b plus prednisolone, the partial pressure of arterial oxygen at rest increased from 65 ± 9 mm Hg at base line to 76 ± 8 mm Hg at 12 months, whereas in the group that received prednisolone alone it decreased from 65 ± 6 to 62 ± 4 mm Hg ($p < 0.001$ for the difference in the change from base line values between the two groups); on maximal exertion, the value increased from 55 ± 6 to 65 ± 8 mm Hg in the group that received combined treatment and decreased from 55 ± 6 mm Hg to 52 ± 5 mm Hg in the group given prednisolone alone ($p < 0.001$). The side effects of interferon gamma-1b, such as fever, chills, and muscle pain, subsided within the first 9 to 12 weeks. **Conclusions.** In a preliminary study, 12 months of treatment with interferon gamma-1b plus prednisolone was associated with substantial improvements in the condition of patients with idiopathic pulmonary fibrosis who had had no response to glucocorticoids alone. (N Engl J Med 1999; 341:1264-9)

Cryptogenic fibrosing alveolitis (CFA) is a restrictive lung disease that typically presents in patients in their late sixties with symptoms of breathlessness and cough.¹ Although a small proportion of patients have relatively stable disease, the clinical course in the majority involves progressively disabling breathlessness, culminating in death from respiratory failure.² The median life expectancy of unselected newly diagnosed patients with CFA is of the order of three years,³ a prognosis similar to that of clinical stage Ib non-small cell lung cancer.⁴ CFA is generally considered to be a rare disease but, depending on the stringency of diagnostic criteria used, probably occurs in somewhere between six and 28 per 100 000 of the population.^{5,6} In the UK there are

currently therefore somewhere between 3500 and 17 000 patients with CFA, and physicians serving a population of 500 000 will have between 30 and 140 cases under their care. CFA is thus a major and life threatening problem for individual patients and is an appreciable burden to those who provide respiratory health services. One of the more frustrating aspects of the management of CFA that both patients and their doctors have to face is the lack of clearly effective treatments for the disease, and a paucity of evidence from randomised, controlled clinical trials on which to determine how best to use the treatments that are available. The recent study by Ziesche and colleagues⁷ demonstrating evidence of clinical improvement in

patients with CFA treated with prednisolone plus interferon gamma-1b relative to prednisolone alone therefore provides an important new contribution to the evidence base for the management of this disease. Their paper also poses interesting questions on the funding of treatment for CFA.

Current treatment for CFA consists of steroids, given either alone or in combination with an immunosuppressant or cytotoxic agent.^{18,9} The first line treatment for CFA recently recommended in guidelines produced by the British Thoracic Society (BTS)¹⁰ and in a consensus statement from the American Thoracic and European Respiratory Societies¹¹ is a combination of prednisolone and either azathioprine or cyclophosphamide. The evidence supporting the use of azathioprine comes primarily from a randomised, double blind, placebo controlled clinical trial in which 27 patients with chronic progressive CFA were randomised to receive either prednisone alone (13 patients), or prednisone plus azathioprine (14 patients).¹² After one year of treatment mortality was similar with the two treatments, with four deaths in each group but, among the survivors, lung function had improved slightly but non-significantly more in the patients treated with azathioprine plus prednisone. The magnitude of this effect was of the order of a 6.5% increase in mean percentage predicted forced vital capacity (FVC) in the azathioprine plus prednisone group, compared with a 1.7% increase in the prednisone only group, but the variation around these means was high and the difference far from statistically significant ($p=0.87$). After one year of treatment therefore, this study had found no conclusive evidence that adding azathioprine to corticosteroids decreased mortality from CFA or influenced the clinical progress of the disease. The evidence that has led to the use of this drug in the treatment of CFA is that, after a period of extended follow up to a total of nine years after randomisation, deaths in the azathioprine plus prednisone group had increased to six and in the prednisone group to 10. With adjustment for age this difference was on the borderline of statistical significance, which leads to the conclusion that azathioprine may reduce longer term mortality from CFA. Azathioprine appeared to be well tolerated in this study, the majority of adverse effects being attributed to prednisone.

The evidence for the use of cyclophosphamide arises from an earlier randomised controlled trial in which mortality at three years was significantly reduced in 21 patients with CFA receiving prednisolone plus cyclophosphamide (three deaths) compared with 22 patients receiving prednisolone alone (10 deaths).¹³ Details of changes in lung function were not presented in this paper but clinical improvement defined in terms of change in one or more of symptom scores, chest radiographic appearances, or lung function tests occurred at any stage of the three year follow up in seven patients receiving prednisolone only and in five patients receiving prednisolone plus cyclophosphamide. As with azathioprine, therefore, the evidence supporting the use of cyclophosphamide in CFA is the significant effect on mortality, not on symptoms or lung function. Unlike azathioprine, cyclophosphamide was associated with a clinically appreciable increase in the occurrence of adverse effects, primarily haematological toxicity, which occurred in approximately one in three patients.

The design of both of these clinical trials involved the placebo controlled assessment of a drug given in addition to corticosteroids, and did not include a placebo control for corticosteroid therapy. This reflects

the fact that in clinical practice, corticosteroids have been the mainstay of treatment for CFA for many years^{18,9,14,15} on the grounds of evidence derived from a series of anecdotal reports and observational studies dating back to the mid 1950s.¹⁵ However, the use of corticosteroids in CFA has never been subjected to a randomised controlled clinical trial, and there is therefore no conclusive unbiased evidence that corticosteroids have any effect on either mortality or morbidity in this disease.^{10,11,15} In the UK, however, corticosteroids are given to 90% or more of patients who receive any active treatment for CFA, comprising the sole treatment in 76%,¹ and are also reported to be the most frequently used treatment for CFA in the USA.^{8,9} The use of corticosteroids to treat CFA is so established in conventional wisdom in Britain that in 1999 the Medical Research Council cited concerns over the ethics of randomising patients to placebo as the major reason for declining a proposal to conduct a randomised placebo controlled trial of corticosteroid therapy in CFA (Medical Research Council, personal communication). Current management of CFA thus depends heavily on the use of a treatment of no proven benefit, sometimes given in combination with one of two drugs that appear to have influenced mortality in the longer term, but not morbidity or lung function in the shorter term. In this context, the emergence of objective evidence of clinical improvement with interferon gamma-1b in patients participating in a randomised clinical trial⁷ is a welcome development.

As in the above trials of azathioprine and cyclophosphamide, Ziesche and colleagues assessed the effect of interferon gamma-1b given as an addition to corticosteroid therapy.⁷ The patients they selected appear to be broadly representative of those who would currently receive treatment in the UK – that is, those with evidence of progressive disease.¹⁰ The entry criteria for their study were histologically confirmed idiopathic pulmonary fibrosis (an alternative term for CFA), a decline in lung function of at least 10% in the preceding 12 months despite continuous or repeated glucocorticoid therapy, and a total lung capacity above 45% of the predicted value. The main criteria used to define the histological diagnosis was the presence of subpleural and periacinar fibrosis, with only minor cellular infiltration. All patients meeting these criteria then received four weeks of high dose (50 mg/day) prednisolone, reducing to 10 mg/day over the next two weeks. Patients in whom this period of treatment was deemed ineffective were then randomised to receive either 200 µg of interferon gamma-1b subcutaneously three times per week in addition to 7.5 mg of oral prednisolone per day, or to prednisolone alone, in an open study. Treatment was continued for one year; the only difference in the treatments administered during that time was that, in the corticosteroid only group, the dose of corticosteroids could be increased to up to 50 mg/day in those with deterioration in lung function or worsening symptoms.

Although the paper does not tell us which measure or measures of lung function were required to have declined by 10% in the 12 months prior to recruitment, and does not define ineffectiveness in relation to the one month period of high dose corticosteroid treatment immediately before randomisation, the impression presented is that these patients had relatively established fibrotic disease that was deteriorating on usual steroid therapy. The authors report that all of the patients had a histological diagnosis of usual interstitial pneumonia (UIP), and the histological and high resolution computerised tomographic criteria given in the paper are

consistent with this diagnosis.¹⁶ UIP is the commonest histological subtype of CFA and is recognised to be chronically progressive, unresponsive to treatment, and usually fatal.¹⁶ The active and progressive nature of the disease in these patients in the presence of usual treatment is further evident from the subsequent 12 month experience in the prednisolone only treatment group, in which total lung capacity (TLC) decreased in all patients by an average of 4% of the predicted value, and partial pressure of oxygen at rest and after exercise decreased in all but one patient. However, in the patients receiving interferon gamma-1b all of these measures of lung function increased during the treatment period to an extent that was significant within the group and in comparison with the prednisolone only group ($p < 0.001$ for all between group comparisons). The magnitude of the within group increase in TLC in the interferon gamma-1b group was an average of 9% predicted, with a mean difference in change between groups of 13% predicted. Effects of similar magnitude on change in FVC and carbon monoxide gas transfer were also reported, but numerical details were not provided in the paper. There were no deaths amongst the patients taking part in the study and no formal quality of life measures were made. However, breathlessness and the ability to carry out activities of daily living at the end of the study were markedly improved in the patients who received interferon gamma-1b, indicating that the improvement in lung function measures was associated with improvement in symptoms and disability.

These findings are remarkable on at least two counts. Firstly, they provide evidence that drug treatment resulted in statistically and clinically significant improvement in lung function and morbidity in patients with CFA. No other treatment has been shown to do this in the context of a randomised, controlled clinical trial. Secondly, the improvement in the group receiving interferon gamma-1b was remarkably consistent across all outcome measures. All of the patients who received interferon gamma-1b were better at the end of the treatment period, whilst nearly all of the prednisolone only group were worse. No other study, randomised or otherwise, has reported such consistent improvement within a prospectively defined group of patients. The study was small, involving only 18 patients in all, and did not include a double blind placebo control for the interferon gamma-1b but, in the light of the consistency and high degree of statistical significance of the differences between the treatment groups, the overwhelming implication of these data is that treatment with interferon gamma-1b was effective in these patients.

This in itself is an exciting and potentially very fruitful advance in current management options. As with any therapeutic development, it is important that the findings of this study are independently confirmed, either in a repeat study of similar design or in the context of a broader clinical trial, and the longer term effects of interferon gamma-1b on morbidity and mortality assessed. It is also important that the contribution of prednisolone in this therapeutic combination is tested to determine whether the beneficial effect of interferon gamma-1b is the same, greater, or less in the absence of prednisolone. It will also be necessary to determine whether the effect of interferon gamma-1b is in fact attributable to the negation of potential adverse effects of prednisolone on the natural history of CFA,¹⁷ and this will involve a placebo controlled trial which might in turn establish, at long last, whether corticosteroids are indeed effective in CFA. The effect of interferon

gamma-1b should also be assessed in relation to other currently used treatments, particularly azathioprine and cyclophosphamide, again providing an opportunity to investigate in more detail the contribution that these drugs make, either alone or in combination with corticosteroids. Even if only some of these studies are carried out, then one major positive effect of the work of Ziesche and colleagues⁷ will have been to cause these questions to be addressed. However, their study is also likely to stimulate interest in other putative treatments for CFA since they have presented evidence that the likely mechanism of the effect of interferon gamma-1b was a reduction in transcription of genes for the production of transforming growth factor β_1 and connective tissue growth factor.⁷ This observation is likely to provide a major stimulus to investigate and develop other agents that can influence the production of these and related growth factors, and progress in this area is likely to be relevant to many disorders in addition to CFA. This, in turn, raises the prospect that CFA and related diseases may become a more economically viable target for investment in pharmaceutical research and development, which would indeed be a major step forward for CFA and perhaps some of the other "orphan" diseases in respiratory and other fields of medicine.

There is, however, one very important and much more immediate practical question that arises from the work of Ziesche *et al*, and this is whether, in clinical practice, patients with CFA should now be treated with interferon gamma-1b. Since the available clinical trial evidence indicates that interferon gamma-1b is clinically effective in this disease, and in terms of improvement in lung function, breathlessness and related morbidity appears to have more to offer in typical patients with CFA than either azathioprine or cyclophosphamide, the logical conclusion is that they should, at least until such time as evidence emerges to the contrary. Indeed, it can be argued that both cyclophosphamide and azathioprine are currently used on the grounds of evidence of efficacy that is no more persuasive than that now available for interferon gamma-1b. Is there any justification for withholding a treatment that was associated with "substantial improvements" in pulmonary ventilation and gas exchange⁷ from patients currently suffering from CFA?

In a covering editorial published alongside the paper, du Bois argued that the findings of pilot studies, however promising, cannot be used as the basis of recommendations for treatment, and in support of this argument cited various concerns relating to the representativeness of the patients in this study relative to patients with CFA in general.¹⁸ Whilst commendable, however, and not disputing the importance of independent confirmation, it is evident that this argument has not discouraged either the widespread use or the adoption into clinical management guidelines of either azathioprine or cyclophosphamide,^{10,11} in both cases on the grounds of single clinical trials involving small sample sizes and producing no evidence of substantial improvement in ventilation or gas exchange.^{12,13} It is therefore arguable that, if the role of interferon gamma-1b needs to be independently confirmed before it is used to treat patients, then so should the roles of azathioprine and cyclophosphamide and, for that matter, corticosteroids. Caveats relating to the representativeness of the patients in this study to the general population of patients with CFA are also important, but the simple solution to these concerns that is widely applied in implementing clinical trial evidence in many areas of medicine is to define the indications for

LEARNING POINTS

- * Interferon gamma-1b treatment over 12 months was associated with clinically significant improvements in lung function and morbidity in patients with progressive CFA also treated with prednisolone
- * This is the first time that statistically significant evidence of improvement in these indices has been demonstrated for any treatment for this condition in the context of a randomised clinical trial
- * The effect of interferon gamma-1b is likely to be mediated by a reduction in transcription of genes for the production of transforming growth factor β_1 and connective tissue growth factor
- * Interferon gamma-1b is expensive and its role in treating CFA therefore needs to be carefully defined
- * Until evidence appears to the contrary, the addition of interferon gamma-1b therapy is probably indicated in patients with progressive, UIP subtype CFA currently treated with corticosteroids.

interferon gamma-1b in clinical practice in absolute or general relation to the entry criteria used for the study. In the event, however, the patients included in the trial by Ziesche *et al*⁷ had fairly typical progressive UIP, and many patients with CFA will fall into this broad category. There is surely no justification for denying treatment to this group simply because other categories of CFA were excluded from the trial.

In a related editorial Egan also questioned the general representativeness of patients able to complete the biopsy requirements of the study, and drew attention to the possibility that the effect of interferon gamma-1b may have been to negate an adverse effect of corticosteroids.¹⁷ Again these are valid concerns, but do not in themselves justify withholding interferon gamma-1b treatment from patients similar to those included in the study and in whom a clinical decision has been made to continue treatment with corticosteroids. Egan also implied that the applicability of the study is limited by low statistical power, but in fact the study detected highly statistically significant effects in spite of the small sample size. Power is not an issue in relation to those clinical end points that were significantly improved in the interferon gamma-1b treatment group, though the small numbers of patients combined with the lower limit on total lung capacity in the entry criteria may explain the low mortality experienced in this study, commented on by du Bois.¹⁸

There is, however, one other factor that may have inhibited endorsement of what appears to be a clinically effective treatment for CFA which is that, at current UK prices, the interferon gamma-1b regimen used in this study would add approximately £27 500 (\$41 000) per year to the cost of treating CFA.¹⁹ This is a substantial cost and, although not inordinately expensive in relation to some chemotherapy agents used to treat lung cancer or to the median cost of \$22 000 per life year saved for tertiary disease prevention interventions in the USA,²⁰ this is in absolute terms an expensive treatment that, if widely implemented, would place a major financial burden on health care providers. Perhaps our unspoken question is whether the substantial im-

provement in lung function and respiratory morbidity in patients with CFA observed in this study justifies this expense. No doubt our patients currently living with CFA would have something to say about that.

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