Interferon-γ1b Therapy in Idiopathic Pulmonary Fibrosis*

A Metaanalysis

Ednan K. Bajwa, MD; Najib T. Ayas, MD MPH; Michael Schulzer, MD, PhD; Edwin Mak, BSC; Jay H. Ryu, MD; and Atul Malhotra, MD, FCCP

Context: **Despite the investigation of multiple therapeutic options, idiopathic pulmonary fibrosis (IPF) remains a devastating, progressively fatal disease. Much interest has focused on the use of interferon (IFN)-γ1b therapy, but the efficacy of this treatment has not been proven.**
Objective: **To determine whether IFN treatment reduces mortality in patients with IPF.**
Design: **A metaanalysis of randomized controlled trials evaluating the use of IFN-γ1b as treatment for IPF.**
Main outcome measure: **Mortality in patients treated with IFN-γ1b was compared to mortality in patients treated with control therapies.**
Results: **A total of three studies involving 390 patients was included in the analysis. IFN-γ1b therapy was associated with reduced mortality (hazard ratio [HR], 0.418; 95% confidence interval [CI], 0.253 to 0.690; p = 0.0003). A comparison of mortality at different time points revealed that IFN-γ1b therapy was associated with significantly reduced mortality at 1 year (0.0861; 95% CI, 0.0244 to 0.1478; p = 0.0063), 18 months (0.1682; 95% CI, 0.1065 to 0.2299; p < 0.0001), 650 days (0.1939; 95% CI, 0.1386 to 0.2492; p < 0.0001), and 2 years (0.2652; 95% CI, 0.1652 to 0.3652; p < 0.0001).**
Conclusion: **When the results of multiple studies are combined in a metaanalysis, IFN-γ1b therapy is associated with reduced mortality.** ***(CHEST 2005; 128:203–206)***

Key words: interferon; lung; pulmonary fibrosis; restriction; survival; treatment

Abbreviations: CI = confidence interval; HR = hazard ratio; IFN = interferon; IPF = idiopathic pulmonary fibrosis

Interstitial pulmonary fibrosis (IPF) is a progressive lung disease of unknown etiology, which is characterized by parenchymal fibrotic changes and by worsening respiratory symptoms and gas exchange. The disease is almost uniformly fatal. Although a number of antiinflammatory and immunosuppressive treatments have been evaluated,[1,2] none has been shown to be efficacious in improving survival or producing other clinically important benefits. Although some of these therapies are still commonly employed in clinical practice, they are associated with substantial adverse effects, which may outweigh any potential benefits provided.[3,4] Indeed, the lack of benefit from antiinflammatory therapies has provoked some investigators to classify IPF as a disease of fibroblastic proliferation rather than an inflammatory disorder.[5]

Recently, much attention has focused on the utility of the T-helper type 1 cytokine interferon (IFN)-γ as a treatment for IPF. The rationale for its use has been based on observations of its properties as an inhibitor of fibroblast proliferation, collagen synthesis and deposition, and expression of profibrotic cytokines.[6–9] In addition, IFN-γ appears to modulate immunity by enhancing host defenses against infection in specific populations and by altering the nature of the inflammatory response.[10–12]

*From the Division of Pulmonary and Critical Care Medicine (Drs. Bajwa and Malhotra), Brigham and Women's Hospital, Boston MA; the Department of Medicine (Drs. Ayas and Schulzer) and the Pacific Parkinson's Research Centre (Mr. Mak), University of British Columbia, Vancouver, BC, Canada; and the Division of Pulmonary and Critical Care Medicine (Dr. Ryu), Mayo Clinic, Rochester, MN.
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Correspondence to: Atul Malhotra, MD, FCCP, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115; e-mail: amalhotra1@partners.org

Previously, a small randomized controlled trial[13] involving 18 patients showed a significant improvement in physiologic parameters resulting from treatment with IFN-γ1b and prednisolone compared with treatment with prednisolone and placebo. However, a more recent randomized controlled trial[14] involving 330 patients failed to show a benefit from IFN-γ1b therapy compared with placebo. Additionally, reports[3,14] have surfaced that suggest there is harm potentially associated with IFN therapy. Thus, there exists substantial controversy regarding the potential role of IFN-γ1b in the treatment of IPF.[15] To update the state of knowledge in this area, we conducted a metaanalysis of data from randomized controlled trials of IFN therapy in IPF. Metaanalysis is a commonly used statistical technique whereby the results of individual studies can be pooled together by weighting them according to their standard errors. Since data from multiple studies are used, the precision of the pooled result is greater than that for each individual study. This technique has been widely used to generate hypotheses for subsequent randomized trials.

Methods and Materials

Literature Search and Identification of Trials

A systematic computerized search was performed using MEDLINE, CINAHL, EMBASE, and the Cochrane Controlled Trials Register. The search terms used were the following: (*pulmonary fibrosis.af* or *usual interstitial pneumonia.af*); and (*interferon.af*) *and* (*clinical trial.pt or randomized controlled trial.pt*). Bibliographies of identified studies and review articles were searched for additional trials. Experts in the field were contacted for information regarding studies that may have been overlooked, and additional information was obtained from presentations at international professional meetings. Studies were included that had results available as of July 2004.

Study Selection

All retrieved information was assessed by two reviewers. Studies were included if they met the following criteria: (1) they were randomized controlled trials with a reasonable control group; (2) enrolled patients met accepted clinical or pathologic criteria for the diagnosis of IPF; (3) IFN-γ was delivered for at least 6 months; and (4) mortality data were reported in the form of a Kaplan-Meier survival analysis.

Statistical Analysis

Information was extracted from Kaplan-Meier survival analyses that were reported in each study. Individual Kaplan-Meier graphs were digitally analyzed and used to compare survival at different durations of follow-up. The pooled differences in survival rates (*ie*, survival in the IFN group − survival in the control group) at five different time periods (*ie*, 6 months, 1 year, 18 months, 2 years, and 650 days) were calculated and compared. Also, the pooled hazard ratios (HRs) were derived from the individual survival curves and were combined according to the methods of Parmar and colleagues.[16]

Results

Description of Studies

Four studies were identified that met the defined inclusion criteria. These included two recently published randomized controlled trials,[14,17] one unpublished study from which data had been presented at professional meetings,[18] and one randomized controlled trial that had originally been published in 1999,[13] with additional long-term follow-up data that had been presented at a professional meeting.[19] Details of these studies are provided below (Table 1). The study by Strieter and colleagues[17] was ultimately not included in our analysis because the data for a Kaplan-Meier survival curve were not available from the lead author. However, only one death occurred in that study, making it unlikely to influence our overall survival data.

Results of Analysis

When the results of the three studies[13,14,18] were combined using metaanalysis, the treatment of IPF with IFN-γ1b significantly decreased the mortality rate compared with control group therapies (pooled HR, 0.418; 95% confidence interval [CI], 0.253 to 0.690; $p = 0.0003$) [Fig 1]. Pooled differences in survival rates were computed for time points for which data were available in each study. There were significant improvements in survival (*ie*, proportion

Table 1—*Details of Included Studies*

Source	Active Treatment	Control Treatment	Patients	Follow-up	Deaths	HR
Ziesche et al[13]	IFN-γ1b 200u TIW	Placebo	9 active 9 control	5 yr	2 active 7 control	0.1796
Antoniou et al[18]	IFN-γ1b 200u TIW Prednisolone 10 mg/day	Colchicine Prednisolone 10 mg/day	27 active 15 control	1.5 yr	2 active 6 control	0.1618
Raghu et al[14]	IFN-γ1b 200u TIW Prednisolone 7.5 mg/day	Placebo Prednisolone 7.5 mg/day	162 active 168 control	1.4 yr	16 active 28 control	0.5898

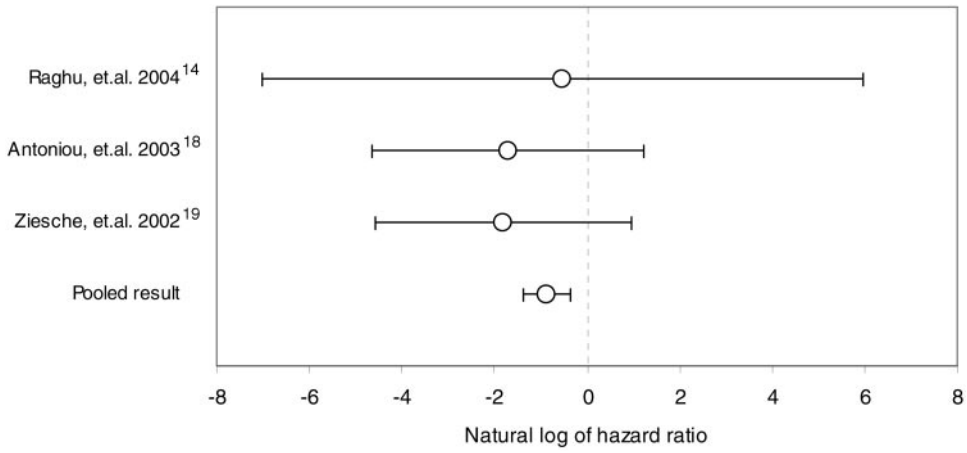

FIGURE 1. Effect of IFN-γ1b treatment on survival. A natural logarithm of 0 for the HR indicates no difference in mortality between the IFN and control groups. A negative value for the logarithm indicates a reduction in mortality rate with IFN. The variances used to construct the CIs for the graph are conservative as they are based on estimates from available Kaplan-Meier analyses rather than the raw data.

survived in IFN arm − proportion survived in control arm) at 1 year (0.0861; 95% CI, 0.0244 to 0.1478; $p = 0.0063$), 18 months (0.1682; 95% CI, 0.1065 to 0.2299; $p < 0.0001$), 650 days (0.1939; 95% CI 0.1386 to 0.2492; $p < 0.0001$), and 2 years (0.2652; 95% CI, 0.1652 to 0.3652; $p < 0.0001$), but not at 6 months (0.0046; 95% CI, −0.0364 to 0.0456; $p = 0.82$). Due to differences in trial design and the limited data available from each trial, subgroup analyses and analyses of outcomes other than survival were not possible. Within individual studies, IFN-γ1b therapy did not have any apparent effect on survival, apart from the long-term (as yet unpublished) results of one small study.[19]

Comment

Treatment of IPF with IFN-γ1b showed significant efficacy in improving overall survival and survival at the time points of 1 year, 18 months, 650 days, and 2 years when compared with control group therapies. The results of this analysis are notable because of the novel finding that IFN-γ1b therapy may be efficacious in improving survival in patients with IPF. As noted earlier, essentially all previous therapeutic studies have failed to demonstrate a significant effect on survival in IPF.

It should be noted that one large study[14] was responsible for the majority of patients included in this analysis. Despite the rigorous trial design, the high rate of medication adherence, and the low dropout rate, a significant result was not found in that study. With the addition of patients from the other studies, a statistically significant improvement in mortality became evident. However, one of the studies included in this analysis has not yet been published, while another relies on unpublished long-term follow-up from a previously reported study. The study by Ziesche and colleagues[13] is unique in that the physiologic improvements associated with IFN-γ1b treatment in that trial have not been replicated to date. Questions have been raised about whether the patients included in the trial were truly representative of a general population of patients with IPF. For example, other studies[4,20] that included patients with lower FVC have not demonstrated a similar benefit. This also raises the possibility that IFN-γ1b treatment may be most beneficial in patients with less advanced disease, as suggested by a subgroup analysis of the largest trial to date.[14] Additionally, the unpublished study included in this report used colchicine in the control treatment arm. While colchicine has been included in treatment algorithms for IPF, no clear benefit has been associated with its use. However, its inclusion in the study could have affected the outcome, for example, by independently causing clinical improvement and biasing the results toward the null hypothesis.[21]

Two of the studies included here utilized corticosteroids as part of their treatment protocol,[13,18] while the third study[14] allowed treating clinicians to utilize some corticosteroids but did not formally include them as part of the protocol. Although the effect of corticosteroids on the pathogenesis of IPF is incompletely understood, therapy using these agents has not been demonstrated to be beneficial,[1] suggesting that they are unlikely to produce a clinically meaningful effect. However, the possibility of an interac-

tion between corticosteroid and IFN-γ1b treatment (for both efficacy and toxicity) has not been excluded. As such, it is possible that our results have been confounded by the fact that corticosteroids were not employed equally in the studies included in our analysis.

Our analysis suggests that when the results of multiple studies are combined in a metaanalysis, IFN-γ1b treatment is associated with decreased mortality. Clinicians should be aware that, despite the results of published randomized trials, the existing data supporting the use of IFN-γ1b for treatment of IPF are more compelling than for any other therapy in patients with this devastating disease, and we think that equipoise remains regarding this therapy. Because we regard metaanalyses to be hypothesis-generating, we anxiously await the results of ongoing randomized controlled trials, which should definitively establish the role of IFN-γ1b therapy. We hope our findings will help to stimulate interest in the referral of patients to such trials.

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