

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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ABSTRACT

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 μ g 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 baseline 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.)

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IDIOPATHIC pulmonary fibrosis is characterized by a fibroproliferative response with only minor signs of inflammation, and it almost always causes rapid fibrotic destruction of the lung.¹ Regardless of treatment, the median survival is four to five years after the onset of symptoms.² The standard treatment for idiopathic pulmonary fibrosis is oral glucocorticoids. However, lung function improves in less than 30 percent of patients who receive this treatment.²

The proliferation of fibroblasts and the accumulation of interstitial collagens are the hallmarks of progressive organ fibrosis.³ In vitro studies have demonstrated that interferon- γ inhibits the proliferation of lung fibroblasts in a dose-dependent manner and reduces the synthesis of protein in fibroblasts.^{4,5} Moreover, in a bleomycin-induced model of lung fibrosis, exogenous interferon- γ down-regulated the transcription of the gene for transforming growth factor $\beta 1$.⁶ This growth factor has been demonstrated to cause severe lung fibrosis in rats with adenovirus vector-mediated overexpression of the cytokine.⁷ It also has a major role in collagen synthesis as well as in the proliferation and activation of fibroblasts. In contrast to the immunomodulatory function of transforming growth factor $\beta 1$, the effects of this growth factor on the regulation of wound healing and fibrosis are mediated by the action of connective-tissue growth factor.⁸ A study of various forms of pulmonary fibrosis, including idiopathic pulmonary fibrosis, has indicated that there may be a general impairment of the production of interferon- γ in patients with pulmonary fibrosis.⁹ In addition, another study reported that treatment of progressive pulmonary fibrosis with interferon gamma-1b was effective in patients who had idiopathic pulmonary fibrosis, scleroderma, or sarcoidosis that was resistant to three months of treatment with high doses of glucocorticoids.¹⁰

On the basis of these observations and the slow turnover rate of connective tissue, we hypothesized that 12 months of treatment with interferon gamma-1b, in combination with prednisolone at a dose that does not affect the clinical course of idiopathic

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pulmonary fibrosis when given alone, would slow or even stop the progression of disease.

METHODS

Patients were eligible for the study if they had histologically verified idiopathic pulmonary fibrosis and if they had had a decrease in lung function of at least 10 percent during the 12 months before the study began, despite continuous or repeated treatment with glucocorticoids, other immunosuppressive agents, or both for at least 6 of the 12 months. The main histopathological feature used to identify idiopathic pulmonary fibrosis was the presence of subpleural and periacinar fibrotic lesions, with only minor cellular infiltration. The absence of bilateral patchy infiltrates on high-resolution computed tomography and the demonstration of a predominantly peripheral distribution of lesions were the radiologic criteria for identifying the disease. Patients with a history of exposure to organic or inorganic dust or drugs known to cause pulmonary fibrosis and those with connective-tissue diseases or other chronic lung diseases causing pulmonary fibrosis were excluded. Patients with end-stage idiopathic pulmonary fibrosis, as identified on the basis of a total lung capacity of less than 45 percent of the predicted normal value, were also excluded.

The study was conducted between May 1996 and February 1998. The protocol was approved by the ethics committee of the University of Vienna Medical School, and all the patients provided written informed consent. The patients were initially treated with 50 mg of oral prednisolone per day for 4 weeks, with subsequent tapering of the dose to 10 mg per day over a 14-day period, regardless of any previous treatment. Complete lung-function tests were performed after the initial four-week period in combination with high-resolution computed tomography. After obtaining additional written consent from the patients, we performed fiberoptic bronchoscopy and obtained specimens of the lung during peripheral transbronchial biopsy for the assessment of gene transcription.

If the additional glucocorticoid treatment was ineffective, the patients were randomly assigned to receive either 200 µg of interferon gamma-1b (Imukin, Boehringer Ingelheim, Vienna, Austria) subcutaneously three times per week plus 7.5 mg of oral prednisolone daily for 12 months or 7.5 mg of oral prednisolone per day alone for 12 months. In the group of patients who were assigned to receive prednisolone alone, the dose could be increased to 25 to 50 mg per day in patients who had deterioration of lung function or worsening symptoms. Lung function was measured at base line and after 3, 6, 9, and 12 months of treatment. Forced vital capacity, total lung capacity, and arterial-blood gases were measured in patients at rest and after maximal exertion to assess lung function, since these measurements correlate well with the extent of lung fibrosis.¹¹ Predicted normal values were derived from the reference values of the Austrian Society of Pulmonary Medicine.¹² Each value represents the best of at least two measurements. Spirometry and body plethysmography were performed with the Autobox DL 6200 (SensorMedics, Vienna, Austria), and blood gas pressure was measured with a gas analyzer (model ABL 510, Radiometer, Copenhagen, Denmark).

For the assessment of the transcription of the genes for transforming growth factor β1, connective-tissue growth factor, and interferon-γ, three transbronchial-biopsy specimens were obtained from the same lung segment before and after six months of therapy. Approximately 1 µg of complementary DNA was used for semiquantitative analysis by the reverse-transcription polymerase chain reaction (RT-PCR). The constitutive control was glyceraldehyde-3-phosphate dehydrogenase. We amplified the genes using the following primers: 5'GCCCTGGACCAACTATTGC3' (sense) and 5'AGGCTCCAATGTAGGGGCAG3' (antisense) for transforming growth factor β1, 5'CCGACTGGAAGACAGT-TTGG3' (sense) and 5'TCATGCCATGTCTCCGTACATCTT3' (antisense) for connective-tissue growth factor, and 5'GCATCG-TTTTGGGTTCTCTTGGCTGTACTGC3' (sense) and 5'CTC-CTTTTTCGCTTCCCTGTTTGTAGTGCTGG3' (antisense) for

interferon-γ. The specificity of the RT-PCR products was controlled by Southern blot hybridization. The RT-PCR assay was carried out in a total volume of 50 µl. Thirty cycles of a hot-start PCR assay were performed on a Perkin-Elmer thermal cycler (model 480, Perkin-Elmer, Norwalk, Conn.). Aliquots were separated by electrophoresis on a NuSieve GTG agarose gel (FMC Bio-Products, Rockland, Me.) and visualized with Vistagreen (Amersham International, Buckinghamshire, United Kingdom).

Analysis of variance was used to compare the mean changes in values from base line to 12 months in the two treatment groups. The data were analyzed descriptively with Report (version 6.0.08, IDV, Munich, Germany) and statistically with Testimate (version 5.2a, IDV).¹³ The model was interpreted only in the case of a nonsignificant result according to Bartlett's test for homogeneity of variance. We used the Wilcoxon rank-sum test of variance for the statistical evaluation of the results of the gene-transcription analysis. All reported P values are two-sided.

RESULTS

We screened 22 patients for the study and excluded 4 because they had end-stage pulmonary fibrosis. All 18 patients initially received 50 mg of oral prednisolone daily for four weeks, and none had a response to this treatment.

Thus, we enrolled 18 patients (17 men and 1 woman, 9 patients in each group). The main symptom related to their lung disease at the time of enrollment was breathlessness on exertion or at rest. None of the patients had clinically significant heart disease. There were no significant differences between the groups at base line (Table 1). All patients completed the study.

During the 1-year study period, total lung capacity decreased, though not significantly, in all nine patients in the group given prednisolone alone, from

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

| CHARACTERISTIC | PREDNISOLONE ALONE (N=9) | INTERFERON GAMMA-1b PLUS PREDNISOLONE (N=9) |
|---|--------------------------|---|
| Usual interstitial pneumonia† | 9 | 9 |
| Biopsy (no. of patients)‡ | | |
| Open lung | 7 | 8 |
| Transbronchial | 2 | 1 |
| Need for supplemental oxygen (no.) | 2 | 3 |
| Breathlessness on exertion (no.) | 9 | 9 |
| Age (yr) | 61.1±6.0 | 60.1±9.9 |
| Duration of symptoms (yr) | 2.6±0.7 | 2.0±0.8 |
| Total lung capacity (% of predicted) | 66±6 | 70±10 |
| Forced vital capacity (% of predicted) | 67±7 | 68±11 |
| Partial pressure of arterial oxygen (mm Hg) | | |
| At rest | 65±6 | 64±9 |
| On maximal exertion | 55±6 | 55±6 |

*Plus-minus values are means ±SD. There were no significant differences between the two groups.

†The diagnosis of idiopathic pulmonary fibrosis was based on histologic assessment and radiologic signs.

‡The diagnosis of idiopathic pulmonary fibrosis was based on the evaluation of specimens obtained by open-lung or transbronchial biopsy.

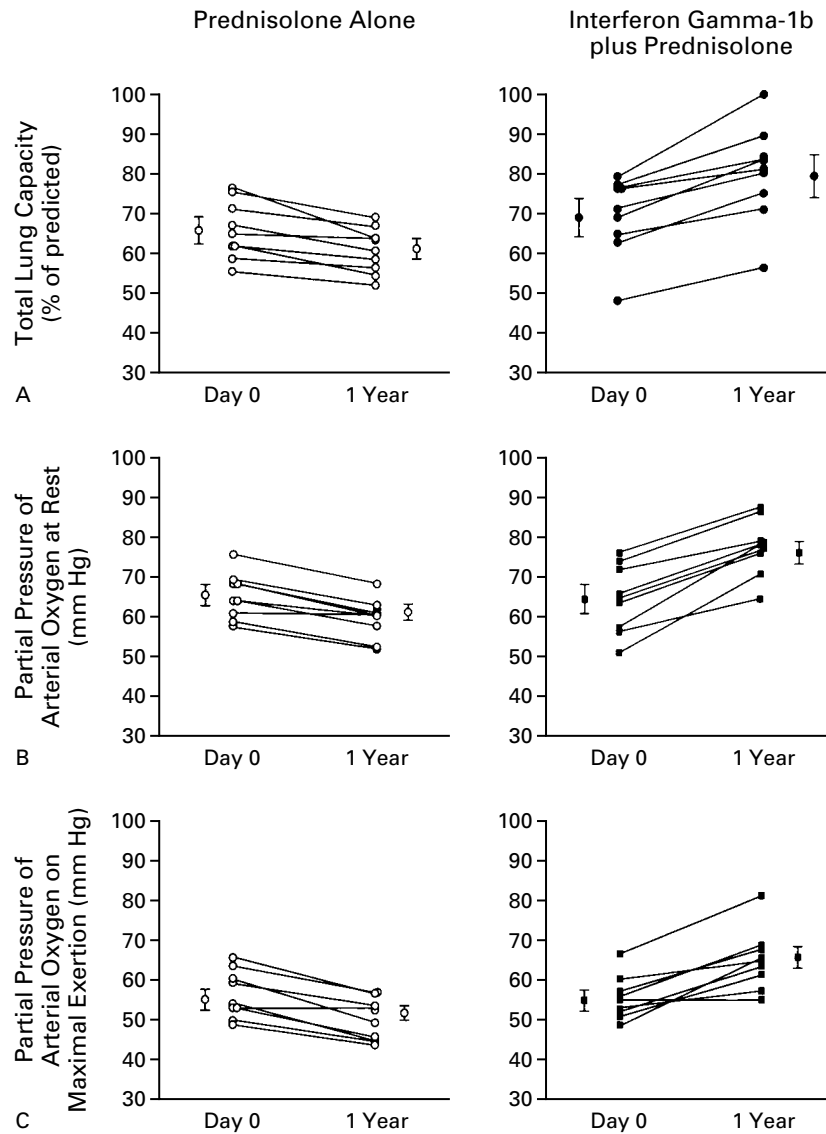


Figure 1. Total Lung Capacity and Partial Pressure of Oxygen before and after One Year of Treatment with Prednisolone Alone or in Combination with Interferon Gamma-1b.

Total lung capacity (Panel A) was measured after the initial four weeks of high-dose prednisolone treatment and before (Day 0) and after one year of treatment. Treatment with prednisolone alone did not significantly affect total lung capacity, whereas the combination of interferon gamma-1b and prednisolone significantly improved it. In contrast with the deterioration in the partial pressure of arterial oxygen at rest (Panel B) and on maximal exertion (Panel C) in the group that received prednisolone alone, pulmonary gas exchange improved significantly in the group that received interferon gamma-1b plus prednisolone. In each panel, individual values for the 18 patients and the mean (\pm SD) value for each group are shown. For each comparison, $P < 0.001$ for the difference in the change from base-line values between the two groups.

a mean (\pm SD) of 66 ± 8 percent of the predicted value at base line to 62 ± 6 percent at 12 months (Fig. 1A). In contrast, ventilation and gas exchange improved significantly in the patients receiving the combination of interferon gamma-1b and prednisolone. In this group, total lung capacity rose from a mean

of 70 ± 10 percent of the predicted value at base line to 79 ± 12 percent at 12 months (Fig. 1A). In other words, the patients receiving prednisolone alone had an absolute decrease in total lung capacity of 4 percent, whereas the group receiving interferon gamma-1b plus prednisolone had an absolute increase in

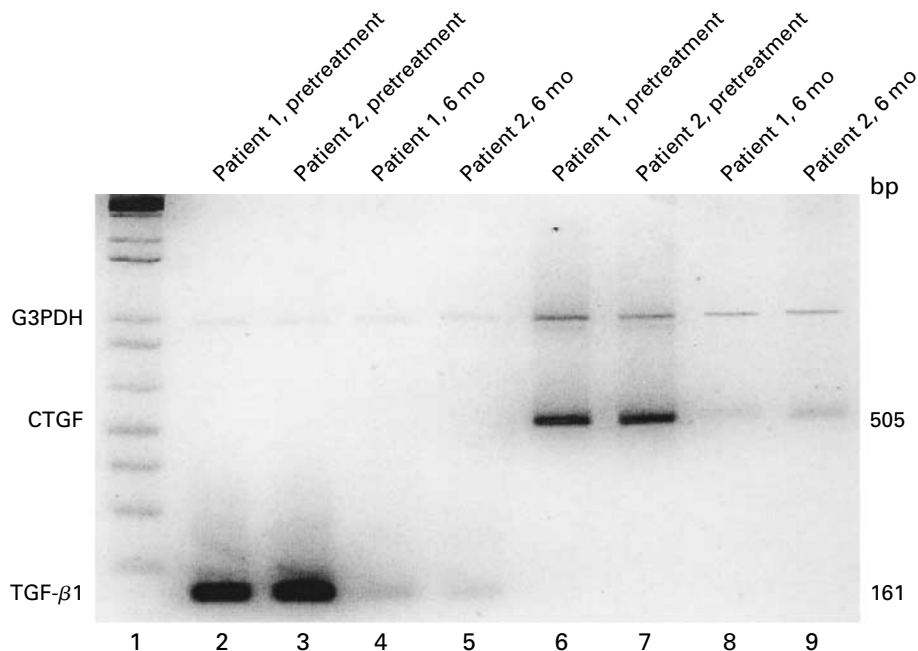


Figure 2. Semiquantitative Assessment of the Transcription of the Genes for Transforming Growth Factor β 1 (TGF- β 1) and Connective-Tissue Growth Factor (CTGF) by the Reverse-Transcriptase–Polymerase-Chain-Reaction (RT-PCR) Assay in Two Representative Patients before and after Six Months of Therapy with Interferon Gamma-1b plus Prednisolone. Three transbronchial-biopsy specimens were obtained from identical lung segments before (lanes 2, 3, 6, and 7) and after (lanes 4, 5, 8, and 9) six months of treatment. PolyA RNA was isolated from a pooled mixture of the three specimens, and the RT-PCR assay was performed to detect transcription of the genes for TGF- β 1 and CTGF. The amplification products of TGF- β 1 and CTGF were 161 bp and 505 bp, respectively, with the amplification product of glyceraldehyde-3-phosphate dehydrogenase (G3PDH, 983 bp) serving as the internal RNA standard. Lane 1 shows the molecular-size marker.

total lung capacity of 9 percent ($P < 0.001$). The results were similar for the changes in forced vital capacity (data not shown). The increase in forced vital capacity and total lung capacity usually started after three months of treatment and was most pronounced over the next three to six months (data not shown).

In the group that received interferon gamma-1b plus prednisolone, the partial pressure of arterial oxygen at rest increased from 64 ± 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) (Fig. 1B). On maximal exertion, the partial pressure of arterial oxygen increased from 55 ± 6 mm Hg at base line to 65 ± 8 mm Hg at 12 months in the group that received interferon gamma-1b plus prednisolone and decreased from 55 ± 6 mm Hg to 52 ± 5 mm Hg in the group given prednisolone alone ($P < 0.001$) (Fig. 1C). There was a similar increase in the carbon monoxide diffusing capacity (data not shown) among the patients receiving interferon gamma-1b plus prednisolone.

As of July 1999, all patients in the study were alive.

After 12 months of treatment with interferon gamma-1b and prednisolone, only one of the three patients who initially required supplemental oxygen was still receiving it. After 12 months of treatment with prednisolone alone, four patients needed supplemental oxygen, as compared with two at base line. After 12 months, all nine patients in the group given prednisolone alone were still breathless on exertion, as compared with only one patient in the group given interferon gamma-1b and prednisolone. All patients receiving interferon gamma-1b and prednisolone reported an improved ability to perform the activities of daily living. However, changes in the quality of life were not formally evaluated.

In an evaluation of the *in vivo* level of transcription of the genes for transforming growth factor β 1, connective-tissue growth factor, and interferon- γ by RT-PCR, we found striking differences before and after six months of therapy with interferon gamma-1b plus prednisolone. Figure 2 shows the results of semiquantitative RT-PCR analysis of the transcription of transforming growth factor β 1 and connective-tissue growth factor in two patients before and after six months of therapy. Figure 3 shows the PCR

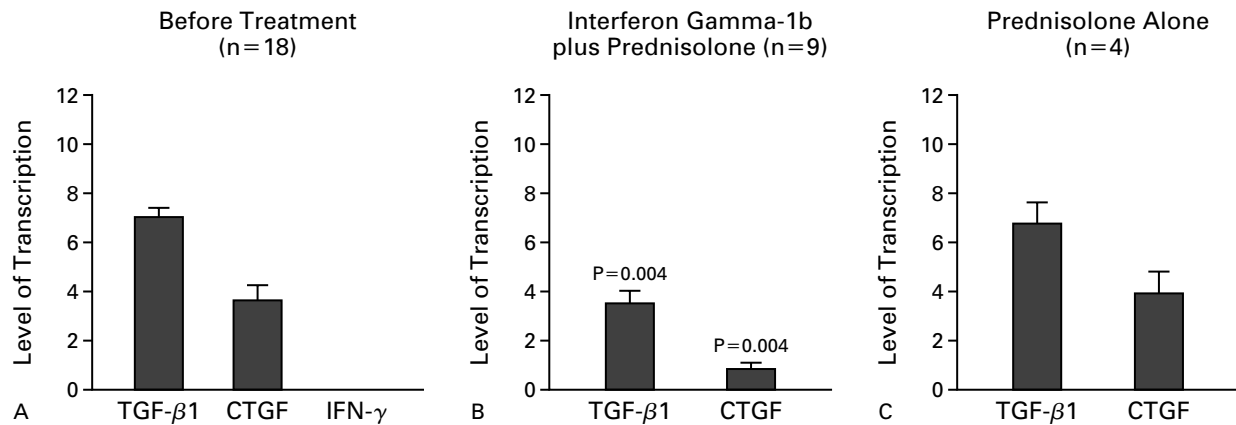


Figure 3. Mean (\pm SD) Level of Transcription of the Genes for Transforming Growth Factor β 1 (TGF- β 1), Connective-Tissue Growth Factor (CTGF), and Interferon Gamma-1b (IFN- γ) before and after Six Months of Treatment.

Data are shown for all 18 patients before therapy (Panel A), for all 9 patients receiving treatment with interferon gamma-1b plus prednisolone (Panel B), and for 4 patients treated with prednisolone alone (Panel C). Analysis was performed on a FluorImager (model 595, Molecular Dynamics, Krefeld, Germany) with ImageQuant software (version 4.2a, Build 13, Molecular Dynamics). Values were compared with those in six normal subjects and are expressed as the number of times above the normal induction value. As compared with the normal levels, the levels of transcription of the genes for TGF- β 1 and CTGF were approximately seven times and four times as high, respectively, in all 18 patients with idiopathic pulmonary fibrosis before treatment. After six months of treatment, the levels of transcription of both genes were significantly diminished ($P=0.004$) only in the group given interferon gamma-1b plus prednisolone. Transcription of the gene for interferon- γ was virtually absent in all patients before treatment.

results obtained after the initial four-week period of treatment with prednisolone but before random assignment to subsequent treatment in all 18 patients, and after six months of treatment in the 9 patients in the group receiving interferon gamma-1b plus prednisolone, and in 4 patients in the group given prednisolone alone who underwent a second bronchoscopy. After the initial treatment with prednisolone, all the patients had levels of transcription of the genes for transforming growth factor β 1 and connective-tissue growth factor that were approximately seven times and four times as high, respectively, as those in six normal subjects, and no transcription of the gene for interferon- γ could be detected. After six months of therapy, levels of transcription of the gene for transforming growth factor β 1 and connective-tissue growth factor decreased significantly only in the group given interferon gamma-1b plus prednisolone ($P=0.004$ for both).

During the first two to three weeks of treatment with interferon gamma-1b plus prednisolone, all nine patients had fever and chills of variable severity, and three had bone and muscle pain. Two patients reported brief, migraine-like headaches. All side effects subsided within the first 9 to 12 weeks of treatment. Fever and chills recurred after an interval of more than three months in two patients with respiratory tract infections. The symptoms resolved within 24 hours after treatment with interferon gamma-1b was discontinued. Treatment with interferon gamma-1b was resumed after two weeks, with no further ad-

verse effects. Repeated laboratory tests showed mild lymphopenia in three patients (1400 ± 500 cells per cubic millimeter; normal range, 1000 to 4000 cells per cubic millimeter). To rule out the possibility that interferon gamma-1b might induce autoimmune disorders, we performed tests for antinuclear antibodies and immune complexes and measured complement activity. However, no elevation of these markers was detected in any of the patients. The main side effects among those who received prednisolone alone were hyperglycemia in three patients, weight gain and skin changes in all patients, and aseptic necrosis of the femur in one patient.

DISCUSSION

In a preliminary study, we found that one year of treatment with interferon gamma-1b plus low-dose prednisolone was associated with substantial improvement of pulmonary ventilation and gas exchange in patients with idiopathic pulmonary fibrosis who had not had a response to glucocorticoids. A larger study is now required to determine whether our results can be confirmed.

Molecular assessment of lung tissue from our patients showed a nearly complete lack of interferon- γ , with levels of transcription of the genes for transforming growth factor β 1 and connective-tissue growth factor that far exceeded the levels in normal tissue. This finding confirms the observation of intense immunohistochemical staining for transforming growth factor β 1 in lung tissue from patients with idiopath-

ic pulmonary fibrosis.¹⁴ Our additional finding of a high level of in vivo expression of both genes supports the idea that connective-tissue growth factor is one of the main mediators of transforming growth factor β 1 during the development of fibrotic lesions. In vitro studies have shown that interferon- γ decreased the synthesis of both collagen I and III¹⁵ and of transforming growth factor β 1.⁶ Moreover, a reduced level of transcription of the gene for transforming growth factor β 1 by adenovirus vector-mediated overexpression of the extracellular-matrix protein proteoglycan decorin resulted in a significant reduction of scarring in a rat model of glomerulosclerosis.¹⁶

The improvement of lung function resulting from treatment with interferon gamma-1b in patients with idiopathic pulmonary fibrosis, in combination with a significantly reduced level of transcription of the genes for transforming growth factor β 1 and connective-tissue growth factor, provides important support for the hypothesis that mesenchymal activation in patients with lung fibrosis depends, at least in part, on the overexpression of the genes for transforming growth factor β 1 and connective-tissue growth factor. Moreover, these data suggest that the mesenchymal activation in patients with idiopathic pulmonary fibrosis corresponds with a low level of transcription of interferon- γ . In view of the well-documented immunosuppressive efficacy of transforming growth factor β 1,¹⁷⁻¹⁹ including the inhibition of the release of interferon- γ ²⁰ and the suppression of interferon- γ -dependent immune reactions,²¹ it is possible that mesenchymal activation during chronic inflammation could lead to an acquired deficiency of interferon- γ . This view is strongly supported by the reciprocal effects of interferon- γ and transforming growth factor β 1 on mucosal inflammation of the intestine.²² Thus, interferon- γ may have a counterbalancing effect on transforming growth factor β 1-dependent activation of mesenchymal tissues.

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CORRECTION

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A Preliminary Study of Long-Term Treatment with Interferon Gamma-1b and Low-Dose Prednisolone in Patients with Idiopathic Pulmonary Fibrosis . On page 1264, in the affiliations paragraph at the bottom of the right-hand column, Dr. Block's e-mail address should have read "lutz-henning.block@akh-wien.ac.at," not "lutz-henning.block@akh-wein.ac.at," as printed.