ERJ Express. Published on April 12, 2006 as doi: 10.1183/09031936.06.00032605

LONG TERM CLINICAL EFFECTS OF IFN-γ-1b AND COLCHICINE IN IDIOPATHIC PULMONARY FIBROSIS

Katerina M. Antoniou[1], Andrew G. Nicholson[2] , Maria Dimadi[3], Katerina Malagari[4] , Panagiota Latsi[5], Angeliki Rapti[3], Nikolaos Tzanakis[1], Rodoula Trigidou[6], , Vlassis Polychronopoulos[7], and Demosthenes Bouros[8]

[1]Department of Pneumonology, Medical School University of Crete, Heraklion, Greece,
[2]Department of Histopathology, Royal Brompton Hospital, London, England,
[3]Department of Pneumonology of ''Sotiria Chest Hospital'' Athens, Greece,
[4]Department of Radiology Medical School University of Athens, Athens, Greece
[5]Department of Pneumonology, Medical School University of Athens, Athens, Greece,
[6]Department of Histopathology, ''Sotiria Chest Hospital'' Athens, Greece,
[7]Department of Pneumonology ''Sismanoglion Hospital'', Athens Greece,
[8]Department of Pneumonology, Democritus Medical School University of Thrace, Alexandroupolis, Greece

Presented in part at the 13th Annual ERS Congress, Vienna 2003 and at the ATS International Conference, Seattle, Washington 2003
Recipient of the Alfred Soffer Award in the Annual ACCP meeting, Orlando, Florida, 25-30 October 2003

CORRESPONDENCE:
Demosthenes Bouros MD, PhD, FCCP
Professor of Pneumonology
Medical School Democritus University of Thrace
68100, Alexandroupolis, Thrace, Greece
Tel and Fax: +30 25510 76106,
Email: bouros@med.duth.gr

KEY WORDS: Interferon gamma-1b, idiopathic pulmonary fibrosis, colchicine, treatment, survival, outcome

ABSTRACT

Idiopathic Pulmonary Fibrosis (IPF/UIP) is a deadly disease with no effective treatment. The purpose of this randomized, prospective, multicenter study was to characterize the clinical effects of IFN-γ-1b administered subcutaneously thrice weekly versus colchicine for two years. This study had not prespecified endpoints.

Fifty consecutive IPF patients were randomized. Patients with mild-moderate IPF were eligible for the study if they had histologically proven IPF or, in the absence of surgical biopsy, fulfilment of the ERS/ATS criteria.

In the intent-to-treat population, 5 of 32 (15.6%) IFN-γ-1b patients and 7 of 18 (38,8%) colchicine patients died (p=0.028) after a median period of follow-up of 25 months Patients treated with IFN-γ-1b had a better outcome after two years of therapy (p= 0.01), and less symptoms as assessed by the St George Questionnaire after 12 months of therapy (p=0.01). Also, IFN-γ-1b group had a higher FVC% predicted (p=0.04) after 24 months of treatment. No significant differences were detected at rest PO_2, TLC % predicted, TL_{CO} % predicted, and HRCT scoring between the two treatment groups.

Our data suggest that long term treatment with IFN-γ-1b may improve survival and outcome in patients with mild to moderate IPF. Further studies are needed to verify these results.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) or cryptogenic fibrosing alveolitis (CFA) is the most common among the idiopathic interstitial pneumonias and has a dismal prognosis (1-3). The median survival of patients with IPF is 3-5 years after the onset of symptoms (4, 5). In this context, it is important to emphasize that this disorder is largely unresponsive to currently recommended combined treatment with corticosteroids and immunosuppressives (1). Therefore, there is a need for novel therapies to reverse or at least limit the lung fibroblast proliferation/activation and the aberrant connective tissue remodelling that characterizes this devastating disease (6, 7).

Interferon gamma (IFN-γ) is a potential therapeutic candidate because it regulates both macrophage and fibroblast functions (6, 8, 9). The theoretical benefits would include diminished expression of insulin-like growth factor 1 (IGF-1), a profibrogenic growth factor produced by macrophages, and suppression of fibroblast proliferation and collagen synthesis (9). A recent study by Strieter et al (10), regarding the effects of interferon gamma-1b (IFN-γ-1b) provides direct evidence that this multifunctional cytokine alters expression of certain molecules postulated, with trends toward a downregulation of fibrotic and angiogenic markers. In addition, IPF seems to be characterized by a predominant expression of T-helper cell (Th) type-2 cytokines and IFN-γ may shift the Th2 balance towards a Th1 profile (11). .

The first observation showing the therapeutic effectiveness of IFN-γ-1b in IPF has been reported by Ziesche et al in a small study (12). Recently, a large clinical trial in US failed to show a beneficial effect on progression-free survival, pulmonary function or the quality of life after one year of treatment (13). However, a subanalysis suggested that patients with less severe pulmonary function impairment had a better

survival. Therefore, there is a need for data verification in a cohort of patients with less advanced disease and for a longer period of treatment.

Colchicine is a well tolerated antifibrotic drug taken orally. Previous studies suggested that its effects are similar to that of prednisone with fewer side effects, while the median survival remained unchanged (14, 15). The rationale for using colchicine is its multiple effects, including the arrest of cell division, the inhibition of granulocytes migration and release of several proteins from cells, and the blocking of the in vitro release of fibronectin from alveolar macrophages (15).

We have, therefore, undertaken a prospective, randomized comparative trial using IFN-γ-1b, taken subcutaneously at a dose of 200 μg three times weekly for 2 years in comparison with colchicine at a dose of 1 mg per day orally, in combination with low dose prednisolone.

MATERIALS AND METHODS

Study subjects

The protocol was approved by the ethics committee of the Institutions. Between March 2000 and June 2003, 68 patients from 8 centres recruited and 50 underwent randomization after informed consent. Patients with mild-moderate IPF were eligible for the study if they had histologically proven IPF (usual interstitial pneumonia, UIP) on surgical lung biopsy, or, in the absence of surgical biopsy, fulfilment of recent American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria (1).

Eligible patients were 40 to 80 years of age, had had clinical symptoms of IPF for at least three months, and had a forced vital capacity (FVC) $\geq$ 55% and $\leq$ 90% predicted value, a carbon monoxide transfer factor (TL_{CO}) that was at least 35 % of the predicted value, and a PaO2 of more than 55 mm Hg, while they were breathing room air at rest.

Newly diagnosed, untreated, symptomatic IPF patients or old-diagnosed IPF patients with a decrease in lung function of at least 10 % despite continuous or repeated treatment with glucocorticoids, other immunosuppressive agents, or both for at least 6 of the 12 months, or evidence of worsening disease on a chest radiograph, or evidence of worsening dyspnea at rest or on exertion within one year before enrolment were included in this study. Patients previously treated with IFN or colchicine were excluded from the study.

Criteria for exclusion were significant history of exposure to organic or inorganic dust or drugs known to cause pulmonary fibrosis and those with connective – tissue disease or other chronic lung diseases causing pulmonary fibrosis, a ratio of the forced expiratory volume in one second (FEV_1) to FVC of less than 0.6 after the use of a bronchodilator, a residual volume that was more than 120 percent of the predicted value, active infection within one week before enrolment, unstable cardiovascular or neurologic disease, uncontrolled diabetes, pregnancy, lactation, any active malignancy likely to result in death or any condition other than IPF likely to result in death within 3 years.

Patients were categorized as non-smokers, current smokers, or ex-smokers (a minimum of one cigarette a day for a minimum of 1 year, stopping at least 6 months before presentation).

Study design

This randomized, multicenter, open-label, parallel group efficacy study started with a run-in consisting of two months period (visits 1-2). The randomisation performed by using a random number table.

This study was originally designed to answer the molecular perspective after both treatment regimens. Because of technical difficulties, this aim was investigated only

in a subgroup of 10 patients (data not shown) and, this study did not have prespecified endpoints.

Our study objectives were to compare the clinical effects of the two treatment regimens after 6, 12 and 24 mo therapy in: the pulmonary function tests (PFTs) (FVC, TLC, TL_{CO} , PO_2 at rest), the extent of lung fibrosis on high-resolution CT (HRCT), the quality of life (St. George's Respiratory Questionnaire), the treatment outcome (using the ERS/ATS criteria), and the overall survival.

During the run-in period, all eligible patients received 50 mg of oral prednisolone per day for 4 weeks, with subsequent tapering of the dose to 10 mg per day over a 1 month period, regardless of any previous treatment. The duration of the treatment was 24-months in 8 visits. If the glucocorticoid treatment was ineffective, the patients were randomly assigned (2 to 1) to receive either 200 μg of IFN-γ-1b subcutaneously three times per week plus 10 mg of oral prednisolone daily for 24 months or 1 mg of oral colchicine per day plus 10 mg of oral prednisolone daily for the same treatment period. No other treatments were allowed during the study. A response to corticosteroids was considered by an increase >10% in FVC% and/or TL_{CO} % predicted. All new symptoms were recorded as adverse events. All patients were followed for the duration of the study regardless of whether they continued IFN-γ-1b or colchicine or not.

Measurements

1. 1. Pulmonary function tests

All patients were evaluated with spirometry and measurements of lung volumes, diffusion capacity and arterial blood gases (at rest).

Spirometry, measurement of lung volumes using the helium dilution technique and the TL_{CO} (corrected for the haemoglobin) using the single-breath method (16) were performed with a computerized system (MasterLab, Jaeger 2.12, Germany). Predicted values were obtained from the standardized lung function testing of the European Community for Steel and Coal Luxembourg 1993 (ECSC) (17). Arterial blood gas determination was done at rest using an arterial blood gases analyzer (AVL330, Switzerland). The partial pressure of O_2 was expressed in units of mmHg.

2. High resolution computed tomography (HRCT) evaluation:

Scoring of disease extent and progression: Two readers, blinded to the clinical, functional data and type of treatment, examined the HRCT images. HRCT slices from five predetermined levels were evaluated (the great vessels, the aortic arch, the carina, the right inferior pulmonary vein, and two centimetres above the right hemidiaphragm).

HRCT extent of disease score: At each level, the overall extent of disease was visually estimated to the nearest 5% including a reticular pattern or ground-glass opacification with or without traction bronchiectasis. To obtain the mean fibrosis score percentages from all slices examined were summed and divided by the number of slices (five). This mean value (range, 0.0% to 100%) was considered the extent of fibrosis, irrespective of the predominant pattern. This visual method of disease extent quantification has been extensively used for HRCT scoring in interstitial lung disease with good functional correlations by Wells and co-workers (18, 19).

HRCT disease progression score: Repeat HRCT studies at twelve months after initiation of treatment were compared to baseline. HRCT changes were measured in a scale of 1 to 5 representing likelihood of improvement or deterioration (HRCT progress score). A score of 1 indicated definite improvement, a score of 2 indicated

that subtle improvement is most likely, a score of 4 was given when subtle or little deterioration was most likely, and a score of 5 when definite deterioration was seen. Stable disease was recorded as 3. This scoring system forms a 5 point scale for disease changes at each HRCT slice (range 5-25 for each patient). To obtain the average HRCT disease progression score the rating values from all slices examined were summed and divided by the number of slices (five).

Definite improvement was agreed to be recognised when unquestionable resolution of ground glass or interstitial abnormalities was seen. Definite deterioration was recognised when unquestionable new areas of ground glass opacities or reticulation emerged or when a microcystic reticular pattern changed into macrocystic disease (coarsening of reticulation to honeycomb) or when unquestionable traction bronchiectasis had developed in an area of previous ground glass opacification. In addition, consensus agreement upon level of "certainty" (either towards improvement or deterioration- notably scores 1 or 5 respectively) was agreed to be also based on the relative predominance of the above signs of improvement or deterioration within each individual slice.

In addition, the extent of emphysema was visually estimated at each level to the nearest 5%, first independently and then by consensus. The mean value (range, 1%–100%) was considered the extent of emphysema.

Finally, a qualitative comment of the type of change was noted including (a) ground glass development or resolution, (b) reticulation development or resolution, (c) coarsening of the reticulation (microcystic reticular pattern replaced by macrocystic disease). The above qualitative parameters were roughly quantitatively characterised overall (20, 21).

3. Outcome

The outcome was evaluated according to the established ATS/ERS criteria (1). A favourable (or improved) and a stable (and presumed favourable) response to treatment were classified as improvement or stabilization of outcome in each separate patient. Symptoms (dyspnea and cough), HRCT and physiologic evaluation (changes in 10% for FVC and TLC, >15% for TL_{CO} and 4 mmHg for PO_2) have been measured in each patient in the different time-points of the study. Symptomatology and PFTs were measured at baseline and at three month intervals and classified into ‘’improved’’, ”stable’’ and ‘’deteriorated’’, according the above criteria (1). The disease progression was evaluated by HRCT after 6 , 12 and/or 24 months of treatment.

In detail, a favourable (or improved), stable or a failure response to therapy is defined by two or more of the following, documented on two consecutive visits over a 3- to 6-mo period, respectively:

a. a decrease, stability or increase in symptoms (dyspnea and/or cough)

b. reduction, stability or increase of parenchymal abnormalities on HRCT scan

c. physiologic improvement, stability or deterioration, defined by two or more of the following: 1.>10% increase in TLC or FVC 2. >15% increase in DLCO 3. an improvement in PO2 (>4 mm Hg increase from the previous measurement).

4. Quality of life

The quality of life of patients was investigated with the St. George’s Respiratory Questionnaire, before and after 12 months of treatment (22, 23).

5. Symptomatology

Assessment of dyspnea was effectuated by the modified Medical Research Council (MRC) dyspnea scale, consisting of a 4-point level of this symptom (24). The status of cough was evaluated at baseline as (dry, productive or absent) and at three month intervals and classified into “improved’’, “stable’’ and “deteriorated’’.

Statistical Analysis

The statistical analysis was carried out using the software SPSS, version 12.0 (SPSS Inc, Chicago IL, USA). Comparisons between and within groups were made using unpaired t test, paired t test, Wilcoxon's rank sum tests, Mann-Whitney U tests or chi-squared statistics as appropriate. Comparisons for the different outcomes (PFTs and QOL parameters) in each time point were made by ANCOVA test for repeated measurements. Survival estimation was made using the Kaplan-Meier analysis. Comparisons of the survival between two groups were made using the Log rank test while Cox regression analysis was used to adjust for possible covariates. A p value of 0.05 or less was considered to indicate statistical significance (25, 26).

RESULTS

Of 68 patients screened, 50 were included in the study and underwent randomization; 32 patients received IFN-γ-1b and 18 colchicine. We excluded twelve patients because they did not meet all the entry criteria and the other six because they responded to corticosteroids. All patients remained in the study until January 2004, unless they were withdrawn because of other reasons (death, clinical worsening, social/personal reasons). Baseline patient characteristics are shown in Table 1. In the first group (IFN-γ-1b) the Incident/Prevalent ratio was 19/13 (Incident cases:59%) and in the second group 12/6 (Incident cases:66%)(p=0.4). No imbalances in the HRCT evaluation were apparent at base line (Table 1). The diagnosis was confirmed by the identification of UIP on surgical lung biopsy in 84% of patients in the IFN-γ group (27 patients) and in 83% (15 patients) in the colchicine group. The median duration of treatment was 20 months in the IFN-γ group (range, 2 to 44) and 15 months in the colchicine group (range, 5 to 44). Clubbing was present in 13 (40.6%) IFN-γ-1b patients and in 9 (50%) colchicine patients (p=0.52).

Survival: Vital status was ascertained in all randomized patients at the time of study completion. In the intent-to-treat population, 5 of 32 (15.6%) IFN-γ-1b patients and 7 of 18 (38,8%) colchicine patients died (p=0.028). The mean survival was 39 months (95 % confidence interval, 35 to 43) for the IFN-γ1b group and 30 months for the colchicine group (95 % CI, 22 to 38) (Figure 1). The hazard ratio for death in the IFN-γ group, as compared with the colchicine group, was 0.30 (95 % CI, 0.07 to 0.86). The Cox regression analysis showed that the difference between the two groups remains statistically significant after adjustment for age and comorbidities (p=0.04). Subanalysis suggested that the effect of treatment on the risk of death depended on the FVC at baseline. Among patients with a baseline FVC above the median ($\geq$71 % predicted) none of the IFN-γ-1bpatients died, as compared with 44 % of the 9 patients in the colchicine group (p=0.008) (Figure 2). Conversely, among 25 patients with a baseline FVC that was <71 % predicted, no survival benefit was apparent (p=0.68). Among patients with a baseline TL_{CO} that exceeded the median ($\geq$51 % of the predicted value) no IFN-γ-1b treated patient died, as compared with 30 % in the colchicine group (p=0.028) (Figure 3).

Respiratory insufficiency or disease progression accounted for 3 of the 5 IFN-γ patients died and for 5 of 7 patients in the colchicine group. The other causes of death were lower respiratory tract infections. Pseudomonas aeruginosa was cultured in two cases.

Outcome: After 6 months of treatment 24 (75%) patients of the IFN-γ group showed improvement or stabilization of their disease as compared with 41% (7 patients) in the colchicine group (p=0.022). After 24 months of treatment 61.9% IFN-γ patients improved or stabilized as compared with 16.7% colchicine patients (p=0.014) (Table 2) . The individual assessment of the three criteria used in this study is shown in Figure 4.

PFTs: No significant differences in lung mechanics, lung volumes, TLco and PO_2 were found after 6 and 12 months of treatment between the two groups (Table 3). A statistically significant difference in FVC% predicted was detected after 24 months of treatment, in favour of the IFN-γ-1b group (Table 3). Mean values of FVC % predicted and PO_2 in three time points of the study are shown in Figure 5.

HRCT scoring: Overall, for the entire cohort of patients (n=50) mean baseline extent of fibrosis at HRCT scoring was (mean±SD) 35.3±10.45%; (range 14-59%). For the IFN-γ-1b treatment group baseline extent of fibrosis at HRCT scoring was (mean±SD) 32.9±8.7% (range 14-48%), and (mean±SD) 40±12.2% (range 23-59%) for the colchicine group. There was no significant difference of the mean HRCT extent of disease score between the groups at baseline (Mann-Whitney U: p=0.184). The mean value of HRCT progress score from both readers was 3.72±0.73 (range 1.9-4.9). There were no differences in progression scores between the two groups after 12 months of treatment in 27 patients treated with IFN-γ-1b and in 14 patients in the colchicine arm (p=0.14). Furthermore, no marked differences were found in disease severity scores between the two groups after 6 months (13 IFN-γ-1b and 9 colchicine evaluated patients, p=0.08) and 24 months of treatment (16 IFN-γ-1b and 5 colchicine evaluated patients, p=0.4).

Symptomatology and quality of life. Neither dyspnea, as assessed by the modified MRC scale, nor cough was different between the two treatment groups at each time point. Nonetheless, the quality of life, according the St. George's Respiratory Questionnaire, was significantly better at month 12 only in the IFN-γ group, as concerning symptomatology (Table 4).

Adverse reactions: Constitutional symptoms, such as fever, myalgia, rigors, headache and flu-like syndrome were significantly more common among patients who received IFN-γ ($p<0.01$), whereas mild diarrhoea was observed only two patients in

the colchicine group. None of the above symptoms was life threatening. In the majority of patients the IFN-γ related symptoms subsided within the first 9 to 12 weeks. Actually, in some of our patients the drug was well tolerated after the first few administrations. Respiratory tract infections were observed in 8 patients in the IFN-γ group and in 2 in the colchicine group. There were 12 recorded hospitalizations, 8 (25%) in the IFN-γ-1b group and 4 in the colchicine group (p=0.8).

Seventeen of the 50 patients (11 in the IFN-γ-1b group and 6 in the colchicine group) discontinued treatment before 24 months. Of the 11 patients in the IFN-γ-1b, 8 stopped because of adverse event and /or disease progression and 3 because of social reasons). Of the colchicine group 6 patients withdrew; 2 stopped because of disease progression and 4 for social reasons.

DISCUSSION

This is the only study in the literature comparing IFN-γ-1b and colchicine. It is also the second largest study exploring the therapeutic role of IFN-γ-1b in patients with IPF. In this well defined patient population, an apparent beneficial effect of IFN-γ-1b in survival, outcome and FVC% predicted after a 24 month treatment comparing to colchicine was observed.

In one hand, the major finding of our study was the apparent survival benefit for the IFN-γ-1b group in comparison with colchicine. A recent retrospective analysis in order to optimize selection of the end point criteria for the Raghu's study (12) showed that mortality was the most inclusive end point for future trials involving IFN-γ-1b (27).

On the other hand, several limitations exist in the design of our study. Firstly, there were no specific endpoint prespecified for this study and hence there were no power calculations made for the sample size. Secondly, but not less importantly, this study

was not a placebo control one. Additional major limitations include the very small group of patients with over 2 years of treatment and the analysis of the lung function data in a limited number of patients remaining in the study for more than 2 years.

On the contrary, no survival benefit was found with colchicine. Our study is the second randomized study that provides data affirming the inefficiency of colchicine in the treatment of IPF. Douglas and coworkers in the first randomised study (28) found that neither prednisone nor colchicine resulted in objective improvement, and the disease continued to progress. Colchicine appears to be a safer alternative to a trial of high-dose prednisone, but may be no different than no therapy (7). The use of colchicine instead of placebo could be a valid alternative in certain cases. With the present data, there is no evidence to suggest a beneficial role for colchicine in the treatment of IPF.

In addition, a rigorous attempt to make an accurate diagnosis was effectuated. A strength of the study is the high percentage (85%) of patients having surgical lung biopsy confirmation of IPF and pathology evaluation following the new classification of idiopathic interstitial pneumonias by an expert pulmonary pathologist. Additionally, duration of follow-up with a mean of 2 years is another strength of this trial as well as the ascertainment of status in all patients in a randomized and multicenter enrolment.

An additional finding of our study is the significant difference of FVC in favour of IFN-γ-1b treatment after 24 months of treatment. Importantly, King et al (27) found that a >10% fall in percentage of predicted FVC was both reliable and predictive of mortality. Moreover, both Collard et al (29) and Flaherty et al (30) identified a decrease of $\geq$ 10% in predicted FVC at 6 months as predictive of mortality in recent reports.

The quality of life was significantly improved in the IFN-γ group using the St Georges respiratory questionnaire, concerning the component "symptoms''. Although this one

is not specific for interstitial lung diseases (23), we have recently demonstrated that SGRQ questionnaire is a sensitive tool for assessing health-related quality of life in IPF patients (31). Interestingly, lung volumes (FVC and TLC) and duration of the disease correlated with SGRQ (31). However, others failed to find any difference (12).

Moreover, although HRCT has been used as one of the multiple parameters (32) to evaluate response to IFN-γ treatment, there was no published study focusing on the longitudinal changes of HRCT features of UIP in patients receiving this treatment. A recently published study showed that extent of reticulation on HRCT is an important independent predictor of mortality in patients with IPF, confirming once more the crucial role of this tool (33). Importantly, the same study provides evidence that treatment assignment to IFN-γ-1b significantly reduced the risk of death in this group of patients (33).

The mechanism by which survival may be prolonged by this pleiotropic cytokine is not clear. Recent findings suggest that mortality in patients with IPF could potentially be altered by IFN-γ-1b through antimicrobial, antiangiogenic, antifibrotic and/or immunomodulatory effects (10). In addition, the better survival in the IFN-γ group may be explained by the mild to moderate disease (median FVC 71% pred, median TLco 51% pred) of our patients and possibly by the longer period of treatment. The recent report by Raghu et al (13), which included patients with more advanced disease, failed to show a survival difference between the IFN-γ and the placebo group. However, a secondary analysis suggested that the effect of treatment on the risk of death depended on the FVC at base-line and that treatment appeared to have had a greater effect on survival among patients with less severe impairment in lung function than among those with more severe disease. These observations indicate that IFN-γ-1b may be beneficial only in patients with mild-to-moderate disease (13).

Two small retrospective, non-comparative (34, 35) and one prospective non-comparative study (36) of IFN-γ therapy for IPF have shown controversial results regarding the usefulness of IFN-γ therapy. Kalra et al could observe symptomatic and functional improvement only in one of the 21 patients treated (34). Similarly, Prasse et al (36) found improvement to physiologic function only in one among five patients. In contrast, Nathan et al. reported that, paradoxically, patients with advanced disease appear to derive the most benefit from IFN-γ therapy (35).

Three patients died in the IFN-γ-1b arm with respiratory failure. As it is already known, data on the natural history of IPF are sparse and the cause of clinical deterioration is often unclear. Disease progression is difficult to distinguish from complications of the disease and adverse effects of treatment. Honore et al (37) reported respiratory failure and alveolar opacities in four IPF patients after initiation of IFN-γ-1b therapy. This possibility is considered more plausible in patients with severe disease (38). Moreover, novel data suggest that rapid respiratory decompensation in patients with mild to moderate IPF is substantially more common than currently perceived (39).

In conclusion, our data suggest that IFN-γ-1b may improve survival and outcome in a well-defined subpopulation of IPF patients. The apparent beneficial role of IFN-γ-1b may be restricted to the patients with mild-moderate disease, based on measurements of pulmonary function tests. Our view is that a long-term administration of IFN-γ-1b is required in order to achieve clinical effects on the disease course. However, the current results should not be overestimated and, because of the limitations of this study, conclusions regarding the treatment effects of IFN-γ-1b cannot be drawn from our results. The results of the ongoing long term clinical trial entitled "I N S P I R E" will hopefully clarify if IFN-γ-1b is efficacious for

patients with IPF.

Acknowledgments

The authors gratefully acknowledge Professors Nikolaos M. Siafakas and Athol Wells for their continuous help in the realisation of this study. We would like to thank Drs Bachlitzanakis N, Lambrakis Ch, Drositis J, Birba G, Mermigkis D, Mermigkis Ch, Lambiri I, Maltezakis G and Meletis G for recruiting and evaluating patients. We particularly thank the histopathologist Anastasios Koutsopoulos for his input in this study.

Supported by an unrestricted grand by Boehringer Ingelheim Hellas, the Society for Pulmonary and Intensive Care Research in the district of East Macedonia and Thrace. The National Health System of Greece paid for both colchicine and IFN-γ-1b.

REFERENCES

1. American Thoracic Society. 2000. Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. International Consensus Statement. Am J Respir Crit Care Med 161: 646-664
2. American Thoracic Society. 2002. ATS/ERS International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 165: 277-304
3. Bouros D: Current classification of idiopathic interstitial pneumonias. Monaldi Arch Chest Dis 2000;55:450-454
4. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157:199-203
5. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164:1171-1181
6. Antoniou KM, Ferdoutsis E, Bouros D. Interferons and their application in the diseases of the lung. Chest 2003;123: 209-216
7. Bouros D, Antoniou KM. Current and future approaches in Idiopathic Pulmonary Fibrosis. Eur Respir J 2005; 16 : 693-703
8. ~~9.~~8. Mason RJ, Schwarz MI, Hunninghake GW, Musson RA.Pharmacological Therapy for Idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1999; 160: 1771-1777
9. Gurujeyalakshmi G, Giri SN. Molecular mechanisms of antifibrotic effect of interferon gamma in bleomycin –mouse model of lung fibrosis: Down regulation of TGF-β and procollagen III GENE Expression and I. Experimental Lung Research. 1995; 21:791-80
10. Strieter RM, Starko KM, Enelow RI, Noth I, Valentine VG. Idiopathic Pulmonary Fibrosis Biomarkers Study Group: Effects of interferon gamma-1b on biomarker expression in idiopathic pulmonary fibrosis patients. Am J Respir Crit Care Med 2004; 170: 133-140

11. Antoniou KM, Alexandrakis M, Sfiridaki K, et al. Th1 cytokines (IL-12 and IL-18) in bronchoalveolar lavage fluid before and after treatment with interferon gamma-1b or colchicine in idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2004; 21: 105-110
12. Ziesche R, Hofbauer E, Wittman K, Petkov V, Block LH. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. N Engl J Med 1999;1264-69
13. Raghu G, Brown KK, Bradford WZ, et al. Idiopathic Pulmonary Fibrosis Study Group: A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004; 350: 125-133
14. Douglas WW, Ryu JH, Schoeder DR. Impact of oxygen and colchicine, prednisone, or no therapy on survival. Am Respir Crit Care Med 2000; 161:1172-1178
15. Addrizzo-Harris DJ, Harkin TJ, Tchou-Wong KM, et al. Mechanisms of colchicine effect in the treatment of asbestosis and idiopathic pulmonary fibrosis. Lung 2002; 180:61-72
16. Official Statement of the American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies: Am Rev Respir Dis 1991; 144: 1202-1218
17. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J, Suppl 1993; 16:5-40
18. Wells AU, King AD, Rubens MB, Cramer D, du Bois RM, Hansell DM. Lone cryptogenic fibrosing alveolitis: a functional-morphologic correlation based on extent of disease on thin-section computed tomography. Am Respir Crit Care Med 1997;155:1367-1375
19. Wells AU, Hansell DM, Rubens MB, Cullinan P, Black CM, du Bois RM. The predictive value of appearances on thin-section computed tomography in fibrosing alveolitis. Am Respir Crit Care Med 1993;148:1076-1082

20. Remy-Jardin M, Giraud F, Remy J, Copin MC, Gosselin B, Duhamel A. Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease: Pathologic-CT correlation. Radiology 1993; 189: 693-698
21. Austin JH, Muller NL, Friedman PJ, et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology 1996; 200:327-331
22. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991; 85 Suppl B: 25-31
23. Bouros D, Psathakis K, Siafakas NM. Quality of life in interstitial lung disease. Eur Respir Rev 1997; 7: 66-70
24. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93: 580-586
25. Kalbfleisch JD, Prentice RL. Statistical Analysis of Failure Time Data. New York: Wiley 1980
26. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002; 359: 1686-1689
27. King TE Jr, Safrin S, Starko KM, et al. Analyses of efficacy end points in a controlled trial on interferon-γ1b for Idiopathic Pulmonary Fibrosis. Chest 2005; 127: 171-177
28. Douglas WW, Ryu JII, Swensen SJ, et al. Colchicine versus prednisone in the treatment of idiopathicpulmonary fibrosis: a randomised prospective study; Members of the Lung Study Group. Am J Respir Crit Care Med 1998; 158: 220-225
29. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538-542

30. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168: 543-548
31. Tzanakis N, Samiou M, Lambiri I, Antoniou K, Siafakas N, Bouros D. Evaluation of health-related quality-of life and dyspnea scales in patients with idiopathic pulmonary fibrosis. Correlation with pulmonary function tests. Eur J Intern Med 2005; 16:105-112
32. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med. 1998;157:1063-72.
33. Lynch DA, David Godwin J, Safrin S,et al; Idiopathic Pulmonary Fibrosis Study Group. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med. 2005;172:488-93
34. Kalra S, Utz JP, Ryu JH. Interferon gamma-1b therapy for advanced idiopathic pulmonary fibrosis. Mayo Clin Proc. 2003;78:1082-1087
35. Nathan SD, Barnett SD, Moran B, et al. Interferon gamma-1b therapy for idiopathic pulmonary fibrosis: an intrapatient analysis. Respiration 2004; 71: 77-82
36. Prasse A, Muller KM, Kurz C, Hamm H, Virchow JC Jr. Does interferon-γ improve pulmonary function in idiopathic pulmonary fibrosis? Eur Respir J 2003; 22:906-911
37. Honore I, Nunes H, Groussard O, et al. Acute respiratory failure after interferon-γ therapy of end-stage pulmonary fibrosis. Am Respir Crit Care Med 2003; 167:953-957
38. Selman M. A dark side of interferon-γ in the treatment of idiopathic

pulmonary fibrosis? Am Respir Crit Care Med 2003; 167:945-946 [editorial].

39. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with Idiopathic Pulmonary Fibrosis. Ann Intern Med 2005; 142:963-967

TABLE 1CHARACTERISTICS OF THE STUDY POPULATION AT ENTRY*

PARAMETER	Group 1 IFN-γ (n=32)	Group 2 Colchicine (n=18)	p-value**
Median (range) age, yr	66 (54-85)	69 (42-82)	
Incident/Prevalent ratio	19/13	12/6	0.4
Sex, n Male Female	 29 3	 13 5	
Smoking Status, n (%) • Smokers • Ex-smokers • Never smokers	 3 (9.4) 16 (50.0) 12 (37.5)	 1 (5.6) 9 (50.0) 8 (44,4)	0.85
Time since first symptom (mo) Duration of treatment, (mo) Follow-up, mo	49.4±24.3 20.25±11.3 28.2±11.1	42.7±16.8 16.3±11 20.3±12.2	0.46 0.24 0.52
FVC, (%pred)	71.8 ± 15.0	70.7 ± 17.7	0.82
TLC, (%pred)	62.8 ± 15.9	63.2 ± 13.8	0.92
TL_{CO}, (%pred)	54.5 ± 18.1	51.1 ± 18.9	0.54
PO_2 (mm Hg)	75.4 ± 17.0	69.5 ± 14.3	0.20
Extent of Fibrosis in HRCT (%)	32.9±8.7	40±12.2	0.18

* Mean values ± SD, unless otherwise indicated.

** p values with the use of independent two sample t-tests in the case of continuous data and chi-square tests in the case of categorical data.

TABLE 2 Outcome at 6, 12 and 24 months of treatment according to ATS/ERS criteria (1).

PATIENTS	Interferon-γ-1b group			Colchicine group		
Time-points	6 mo (32 pts)	12 mo (29 pts)	24 mo (21 pts)	6 mo (17 pts)	12mo (11pts)	24 mo (12 pts)
Improvement or stability	24 (75%)*	18 (62%)	13(62%)**	7 (41%)	5 (45%)	2 (17%)
Deterioration	8 (25%)	11(38%)	8 (38%)	10 (59%)	6 (55%)	10 (83%)

* p=0.02 for the two study groups, ** p=0.01 for the two study groups.

TABLE 3 Comparison of the mean changes (Δ) and their 95%CI of the FVC, TLC, DLCO and PaO_2, at 6, 12 and 24 month time intervals from the baseline values of the two

groups using ANCOVA test (negative and positive values represent deterioration and improvement of baseline respectively).

	IFN-γ-1b x (95%CI), [n]	Colchicine x (95%CI), [n]	*P*
ΔFVC (% of pred)			
Time (months)	-1.3(-3.9 to 1.3), [28]	-1.9(-3.7 to 3.9), [17]	0.7
6	-1.6(-5.2 to 2), [25]	-9.3(-15.9 to -2.6), [11]	0.06
12	1.7(-2.4 to 5.7), [13]	-7.1(-18.7 to -4.5), [5]	0.04
24			
ΔTLC (% of pred)			
Time (months)	-0.4(-4.2 to 3.4), [25]	-4(-12 to 3.9), [17]	0.4
6	-2.3(-6 to 1.4), [24]	-6.8(-16 to 2.8), [11]	0.5
12	-1.7(-9 to 5.6), [13]	1 (-8.6 to 10.6), [5]	0.2
24			
ΔDLco (% of pred)			
Time (months)			
6	-0.5(-4.4 to 3.4), [25]	2.3(-2.9 to 7.5), [16]	0.5
12	-1,5(-7 to 4), [24]	0.96(-9.4 to 11.4), [10]	0.8
24	-6.8(-13 to -0.3), [13]	1.2(-20.7 to 23), [5]	0.3
ΔPaO_2 (mmHg)			
Time (months)			
6	-2.9(-7.4 to 1.4), [28]	-1.8(-4.7 to 1), [17]	0.7
12	-4.9(-8.6 to -1.2), [25]	-5.9(-12.5 to 0.7), [11]	0.1
24	-2.4(-11.4 to 6.6), [12]	-3.9(-13.3 to 5.5), [5]	0.1

TABLE 4 Comparison of the mean changes (Δ) and their 95%CI of the Symptoms, Activity, and Impacts section of SGRQ as well as of the total score, before treatment and after 12 months of treatment of the two groups using ANCOVA test (positive and negative values represent deterioration and improvement of baseline respectively)

	IFN-γ-1b x (95%CI), [n]	Colchicine x (95%CI), [n]	*P*
ΔSGRQ (score)			
Δ(Symptoms)	-13.2(-21.4 to -5), [20]	7.5(-4.5 to 19.5), [7]	0.01
Δ(Activity)	-4.8(-12.7 to 3), [20]	4.7(-12.1 to 22), [7]	0.3
Δ(Impacts)	-1.9(-9.2 to 5.4), [20]	4.1(-6.4 to 14.6), [7]	0.3
Δ(Total Score)	-4.7(-11.4 to 2), [20]	4.8(-5.9 to 15.5), [7]	0.3

LEGEND FOR FIGURES

Figure 1: Kaplan-Meier survival curve among patients with IPF.

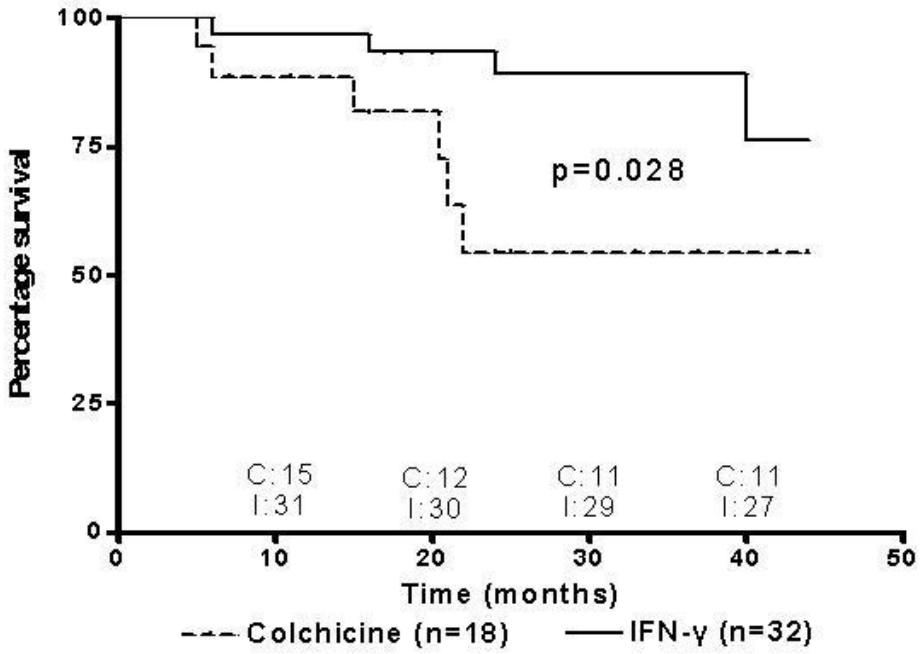

Figure 1

Figure 2: Kaplan-Meier survival curve among IPF patients with FVC% >71%

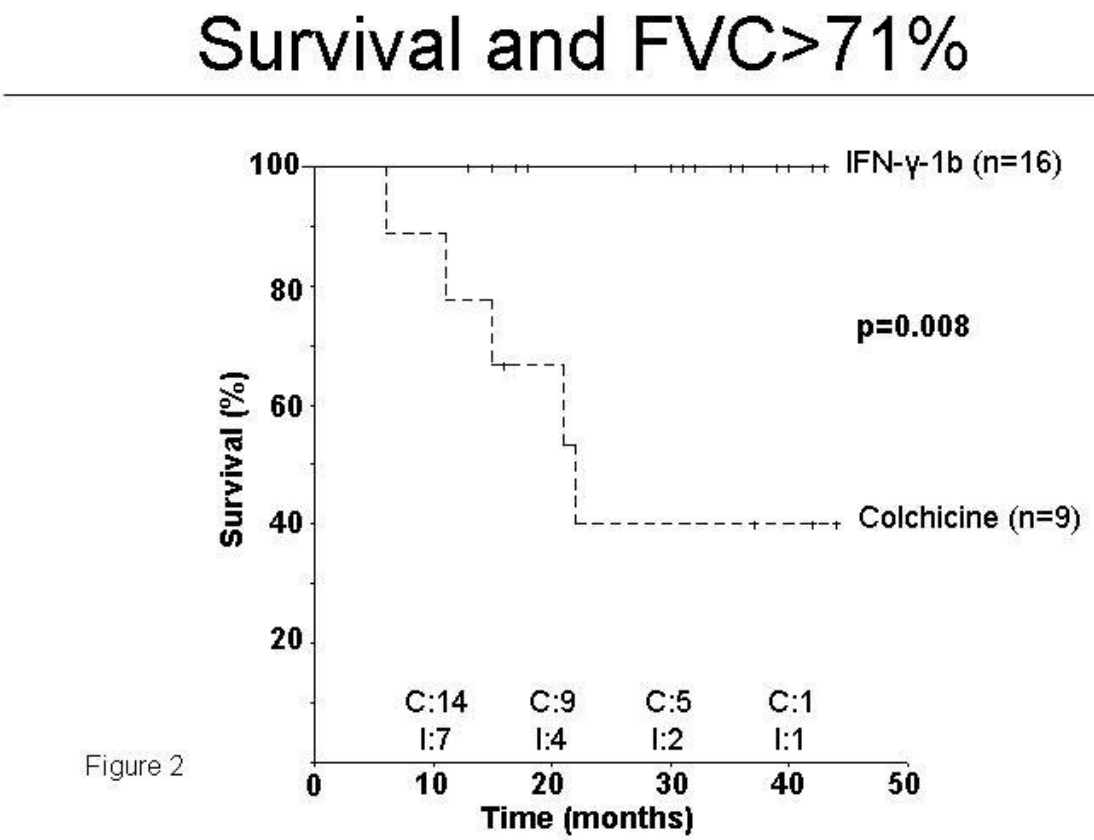

Figure 2

Figure 3: Kaplan-Meier survival curve among IPF patients with TL_{CO} >51%

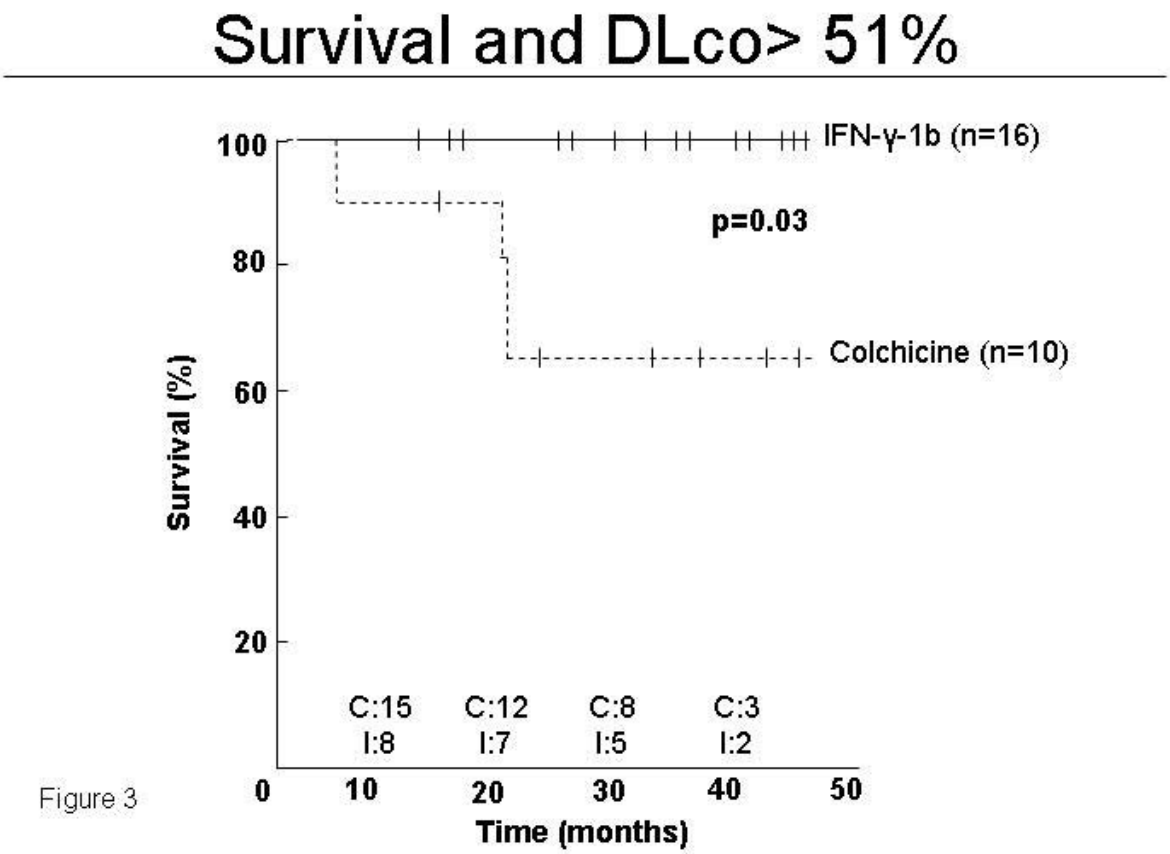

Figure 3

Figure 4: Improvement/stability or deterioration of HRCT score, Dyspnea scale and PFTs/PO2 in IPF patients receiving IFN-gamma-1b (open squares) and Colchicine (closed circles) at 6, 12 and 24 months of follow-up.

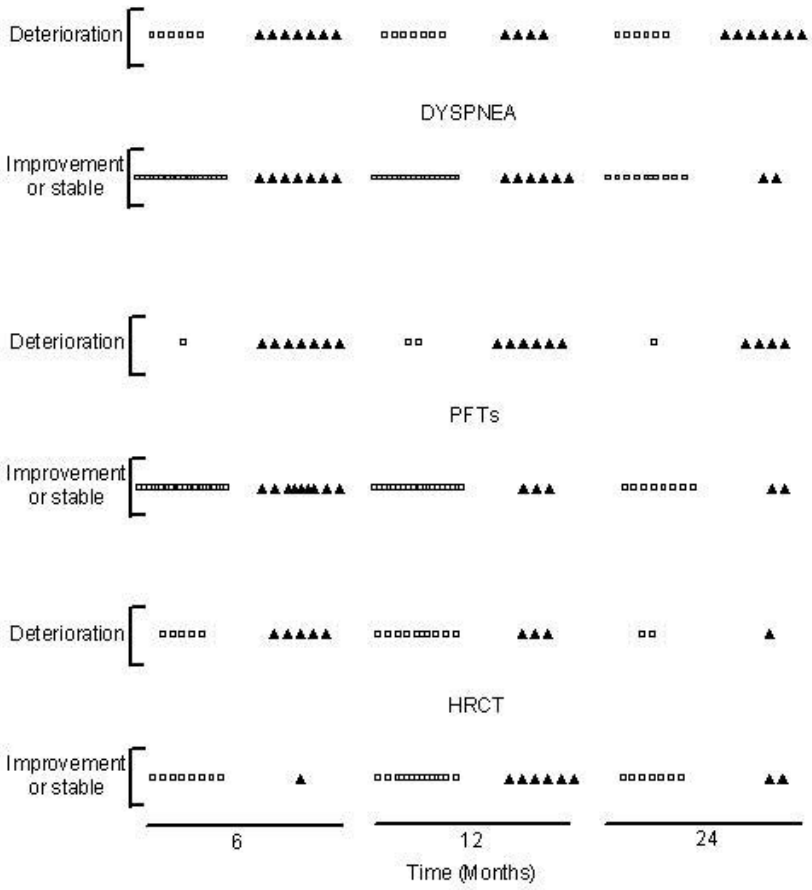

Figure 4

Figure 5: Individual values of FVC% predicted and PaO_2 in IFN-gamma-1b (closed circles) and in Colchicine (open circle) group at 6, 12 and 24 months interval.

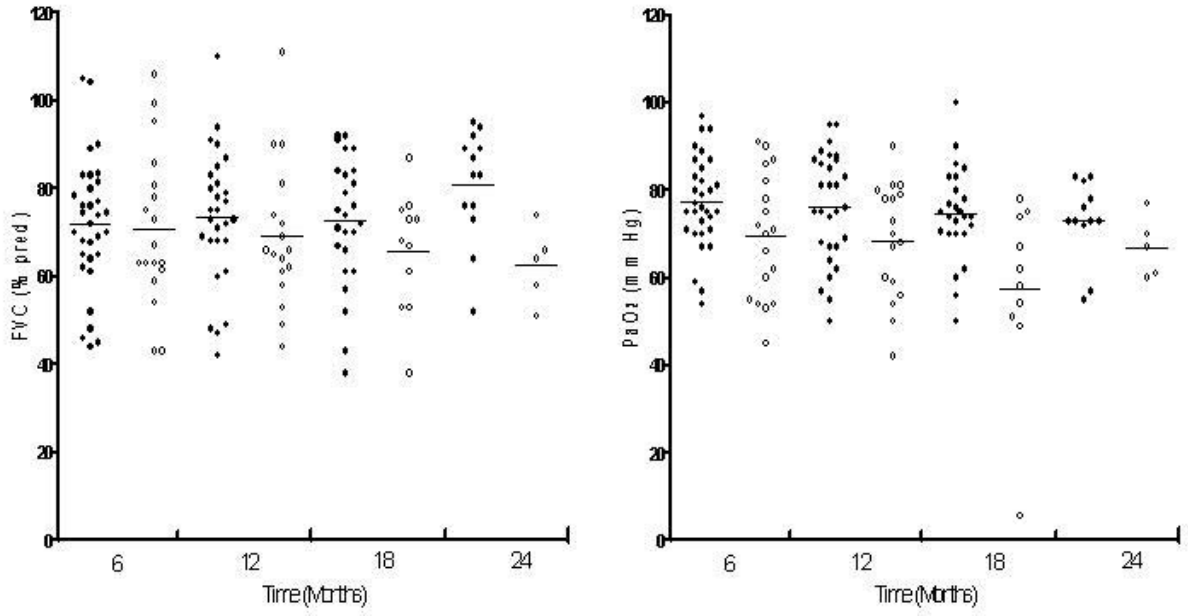
FVC (% pred)
120
100
80
60
40
20
0
6
12
18
24
Time (Months)
PaO2 (mm Hg)
120
100
80
60
40
20
0
6
12
18
24
Time (Months)

Figure 5